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PHARMACOLOGY

AND

THERAPEUTICS

Originally Written by

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THIRTEENTH EDITION, THOROUGHLY REVISED

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Reprinted
April 1947
November 1947

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PREFACE TO THE THIRTEENTH EDITION

When the first edition of this book appeared, in 1899, it was recognized as being "the first severely critical, rigorously scientific, general text-book to be written in English by an experimental pharmacologist." For a quarter of a century successive editions from Cushny's master hand played an important part in sifting and promulgating the advances in knowledge of the subject with which it deals. In the preface to the eighth edition (1924) he quoted prophetically from "the Schoole of Salerne" (1607) the farewell verse:

> And here I cease to write, but will not cease
> To wish you live in health, and die in peace;
> And ye our Physicke rules that friendly read,
> God grant that Physicke you may never need.

When Cushny himself "ceased to write," Professor C. W. Edmunds of the University of Michigan and Professor J. A. Gunn of the University of Oxford were entrusted with the task of preparing the ninth, tenth, eleventh and twelfth editions. These eminent pharmacologists maintained, not merely the critical spirit of the book, but the text as far as was possible. Their success is evidenced by the way in which the book has maintained its popularity with teachers and students.

Since the appearance of the last edition in 1940 Professor Edmunds has died and Professor Gunn has resigned, which necessited the appointment of the present editors to prepare the present revision. We have attempted to bring the subject matter up-to-date with as little violence as possible to the original spirit of the text.

Pharmacology during recent years has undergone notable advances particularly in the fields of chemotherapy, endocrinology, and the vitamins. We have incorporated into the present edition these changes while retaining those features which characterized the original "Cushny." It has been our purpose to prepare a text-book for the student and practitioner of medicine rather than a compendium of pharmacological knowledge. Some of the older material on the effect of drugs on isolated organs or the anesthetized animal, which formed the mainstay of classical pharmacology, has been deleted in favor of the more practical therapeutics of modern medicine. We feel that it is only by emphasis on the scientific basis of therapeutics that modern pharmacology can assume the important rôle in the medical curriculum which it merits.

The present edition incorporates changes introduced by the publication of the twelfth decennial revision of the Pharmacopeia of the United States (1942), the British Pharmacopeia of 1932, and their respective supplements.

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No strictly scientific or completely logical arrangement of the heterogeneous group of substances used as drugs is yet possible. Drugs grouped together by reason of possessing a common pharmacological action may differ from one another in respect of other pharmacological actions; drugs used for a specific therapeutic purpose may have little otherwise in common either chemically or pharmacologically. In spite of this, the subject can be made more intelligible and repetition can be avoided by such arrangement as is possible. In this book drugs are grouped together sometimes because they act at a common point, *e. g.*, hypnotics; sometimes because they have a common therapeutic use, *e. g.*, anthelmintics; and sometimes because of a chemical similarity, *e. g.*, heavy metals. When in doubt, we have decided the arrangement with a view to convenience in teaching the subject and ease of learning it.

In compiling the references at the end of each section we have contented ourselves, as was Cushny's practice, with giving such references as either indicate pioneer researches on a particular subject or as contain in themselves a good bibliography.

A. G.
D. S.

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ARTHUR ROBERTSON CUSHNY

(1866–1926)

Dr. Arthur R. Cushny was born at Fochabers, Scotland, on March 6, 1866. He was educated at the local school and subsequently at the University of Aberdeen, where he graduated M.A. in 1886 and M.B.C.M. (with highest honors) in 1889. Under tenure of a fellowship awarded by his University, he worked for a year at Berne under the celebrated physiologist, Hugo Kronecker, and later at Strassburg under Oswald Schmiedeberg, then the most distinguished pharmacologist in Europe. After acting for two years as assistant to Schmiedeberg, he was invited to succeed J. J. Abel in the chair of Pharmacology at Ann Arbor. Here he remained until 1905, when he returned to England to become the first occupant of the chair of Pharmacology at University College, London, and in 1918 succeeded Sir Thomas Fraser at Edinburgh, where he remained until his sudden death in 1926.

One of his most important contributions to medical science was his research upon the pathological physiology of the mammalian heart, and especially his study of the cardiac arrhythmias. These studies led him to conclude that auricular fibrillation was probably a cause of certain forms of cardiac irregularities which were seen in the human subject. As is well known, this theory was later shown to be correct by studies carried out upon patients by workers in various parts of the world.

Other outstanding contributions were his study of the action of the digitalis glucosides, culminating in his monograph, "The Action and Uses in Medicine of Digitalis and Its Allies," 1925; his investigations of the function of the kidney and the action of diuretics, leading up to the critical summary, "The Secretion of Urine," published in 1917. His quantitative study of the action of the optical isomers was made the subject of the Dohme Lectures, delivered at Johns Hopkins University in 1925, under the general title, "Biological Relations of Optically Isomeric Substances." Apart from these major interests, he made a large number of important researches covering a wide field of pharmacological inquiry, as shown by the bibliography which appeared in the *Journal of Pharmacology and Experimental Therapeutics* (**27**, 265, 1926).

Dr. Cushny possessed to an unusual degree a constructive and original mind with balanced and critical judgment. These qualities added to his unswerving love and pursuit of truth, the breadth and accuracy of his knowledge, and his power of gaining the affections of his fellow workers all over the world, made him one of the most influential figures in the great advances of pharmacology in the first quarter of the twentieth century.

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CONTENTS

INTRODUCTION

Method of Action of Drugs 15
Stimulation, Depression, Irritation 15
Distribution and Concentration 17
Elective Affinity of Drugs. Protoplasm Poisons 18
Local, General and Remote Actions 18
General Theories of Pharmacological Action 19
Chemical Constitution and Pharmacological Action 20
Pharmacological Syndromes 21
Chemotherapy 22
Conditions Modifying the Effects of Drugs 23
Methods of Administration 29
The Chemical Characters of Drugs 33
The Pharmacopœias and Pharmacopœial Preparations 35
Biological Assay 38
Preparations in the U.S.P. Requiring Biological Assay 39
Preparations in the B.P. Requiring Biological Assay 40

PART I

THE ACTION OF INORGANIC SUBSTANCES

I. Water and Salts 43
1. Water 48
2. Sodium Chloride 52
3. Saline Diuretics 53
II. Salts of the Alkalies 53
1. Potassium Salts 53
2. Lithium, Cæsium, Rubidium 55
3. Ammonium 56
III. Salts of the Alkaline Earths 59
1. Calcium 59
2. Barium 64
3. Strontium 64
4. Magnesium Salts 65
IV. Miscellaneous Anions 66
1. Phosphates 66
2. Oxalates 67
3. Fluorides 68
4. Sulfides 68
5. Iodides and Iodine 70
V. Alkalies 78
1. Hydrates and Carbonates of the Fixed Alkalies 78
2. Acetates, Lactates and Citrates 83
3. Ammonia and Carbonate of Ammonia 85
VI. Acids 86
VII. Oxygen 92

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VIII. Carbon Dioxide 96
IX. Carbon Monoxide 99
X. Helium 100
XI. Heavy Metals and Metalloids 100
A. Metals 100
I. Iron 107
II. Copper 115
III. Zinc 118
IV. Aluminum 121
V. Lead 123
VI. Silver 131
VII. Mercury 135
VIII. Minor Metals 147
B. Metalloids 154
I. Bismuth 154
II. Antimony 160
III. Arsenic 165
IV. Organic Arsenic Combinations 177
V. Phosphorus 187

PART II

SUBSTANCES WHICH ARE CHARACTERIZED CHIEFLY BY THEIR LOCAL ACTION

I. Skin and Mucous Membranous Protectives 191
1. Demulcents 191
2. Emollients and Protectives 193
II. Skin Irritants and Counter-irritation 197
1. The Turpentine Oil Group 202
2. Mustard 203
3. Cantharidin 204
4. Toxic Skin Irritants 205
III. Volatile Oil Series 207
1. Camphor 209
2. Malodorous Oils 213
IV. Drugs Affecting Taste 214
1. Sugar 214
2. Flavoring Substances 215
3. Volatile Oils Used as Flavoring Agents and Carminatives . . 215
4. Simple Bitters 218
5. Pepper Group 220
V. Digestive Ferments 220
1. Pepsin 220
2. Pancreatic Ferments 221
3. Vegetable Ferments 221
4. Diastase 222
5. Bile and Bile Salts 222
VI. Vegetable Astringents—Tannic Acid Series 224
1. Charcoal 227
VII. Purgatives 228
1. Mild Aperients, the Castor Oil Group 231
2. The Anthracene Purgatives and Phenolphthalein 233
3. The Jalap and Colocynth Group 236
4. Saline Cathartics 239

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PART III

SUBSTANCES CHARACTERIZED CHIEFLY BY THEIR ACTION AFTER ABSORPTION

A. Depressants of the Central Nervous System . . . 249
I. Narcotics of the Methane Series . . . 249
1. Alcohol–Chloroform Group . . . 249
II. General Anesthetics . . . 269
1. Ether and Chloroform . . . 269
2. Nitrous Oxide . . . 295
3. Ethylene . . . 300
4. Cyclopropane . . . 303
5. Tribromoethanol (Avertin) . . . 305
III. Sedatives and Hypnotics . . . 310
1. Chloral Group . . . 310
2. Barbituric Acid Group . . . 316
IV. Opium Series . . . 329
V. Other Analgesics . . . 358
VI. Cannabis . . . 361
VII. Apomorphine . . . 363
VIII. Bromides . . . 366
IX. Anticonvulsants . . . 373
B. Stimulants of the Central Nervous System . . . 379
I. Strychnine . . . 379
II. Picrotoxin . . . 389
III. Other Analeptics . . . 392
Metrazol and Nikethamide . . . 392
IV. The Xanthines . . . 393
Caffeine, Theobromine and Theophylline . . . 393
Coffee and Tea . . . 402
Minor Diuretics . . . 403
C. Local Anesthetics . . . 404
I. Cocaine . . . 404
II. Other Local Anesthetics . . . 411
D. Curare Group . . . 423
I. Curare . . . 423
II. Intocostrin . . . 426
III. Other Curarizing Drugs . . . 427
E. Substances Acting on the Autonomic Nervous System . . . 429
I. Nicotine Group . . . 429
Tobacco . . . 438
II. Substances Stimulating Parasympathetic Activity . . . 440
1. The Muscarine Group . . . 440
2. Choline, Acetyl-choline and Other Choline Esters . . . 444
3. Physostigmine and Neostigmine . . . 451
4. Pilocarpine . . . 459
III. Substances Depressing Parasympathetic Activity . . . 463
1. The Atropine Series . . . 463
2. Other Synthetic Substitutes for the Belladonna Alkaloids 482
IV. Sympathomimetic Drugs . . . 485
1. Epinephrine (Adrenaline) . . . 485
2. Ephedrine . . . 497
3. Benzedrine . . . 500
4. Other Sympathomimetic Drugs . . . 502
F. Ergot and Its Alkaloids . . . 507
G. The Histamine Group and Anaphylaxis . . . 519

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H. Drugs of Internal Secretion 526
I. Pituitary Anterior Lobe 527
II. Pituitary Posterior Lobe 531
III. Thyroid Gland 540
Thiouracil 548
IV. Parathyroid 549
Dihydrotachysterol 552
V. Adrenal Cortex 553
Desoxycorticosterone 554
VI. Insulin 558
Alloxan 563
II. T he Sex Hormones 563
1. The Gonadotropins 564
2. The Female Sex Hormones 564
The Estrogens 564
Progesterone 570
3. The Male Sex Hormones 571
I. Hematics 573
1. Liver and Liver Preparations 573
2. Stomach Preparations 578
3. Pentnucleotide 579
4. Anticoagulants 580
5. Coagulants 582
J. Vitamins, or Accessory Food Substances 583
K. The Digitalis Series 612
L. The Nitrites 642
M. Minor Drugs and Poisons 650
I. Miscellaneous Drugs 650
1. Chaulmoogra Oil 652
2. Aconite 652
3. Veratrine 654
4. Saponin, Sapotoxin and Solanine 656
5. Hydrastine and Hydrastinine 657
6. Aspidosperma or Quebracho 659
7. Phlorhizin 659
II. Poisons Which Increase Metabolism 660
1. Dinitrophenol 660
2. Tetrahydronaphthylamine 661
III. Poisons Which Act on the Blood 661
1. Nitrobenzol Compounds 661
2. Toluylendiamine 662
3. Benzol 662
IV. Hydrocyanic or Prussic Acid 663
N. Colchicum 666
O. Cinchophen and Its Derivatives 669
P. The Antipyretics. (Acetanilide and Antipyrine Series) 673
Agranulocytosis 676
Q. Salicylates 687
Benzoic Acid and Benzoates 696
R. Quinine and Other Antimalarials 697
I. Quinine 697
II. Quinidine 708
III. Quinacrine (Atabrin) 711
IV. Pamaquine 714
V. Other Antimalarial Drugs 716
S. Emetine and Other Antiamebic Drugs 717
I. Emetine (Ipecacuanha) 717
II. Carbarsone 722
III. Hydroxyquinoline Derivatives 723
1. Chiniofon 724
2. Vioform 724
3. Diodoquin 724

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T. Sulfanilamide and Its Derivatives 725
U. Penicillin and Other Antibiotics 743
I. Penicillin 743
II. Streptomycin 751
III. Tyrothricin and Other Bacterial Antibiotics 753
IV. Other Antibiotics 753

PART IV

ANTHELMINTICS

Anthelmintics 757
I. Male Fern (Aspidium, Filix-mas) 758
II. Pelletierine 759
III. Thymol 760
IV. Chenopodium 760
V. Santonin 761
VI. Carbon Tetrachloride 764
VII. Tetrachlorethylene 766
VIII. Hexylresorcinol 766
IX. Gentian Violet 767
X. Phenothiazine 767
XI. Leche de Higuerón (Ficin) 767

PART V

ANTISEPTICS AND DISINFECTANTS

Antiseptics and Disinfectants 771
I. Surgical Antiseptics and Disinfectants 777
1. Soaps and Other Detergents 777
2. Alcohols 778
3. Carbolic Acid (Phenol) 778
4. Substituted Phenols 782
5. Other Aromatic Surgical Disinfectants 785
6. Mercuric Chloride and Other Inorganic Mercury Compounds 785
7. Organic Mercurials 787
8. Silver and Other Metallic Disinfectants 788
9. Oxidizing Disinfectants 790
10. Boracic Acid and Borax 792
11. Potassium Chlorate 794
12. Iodine 796
13. Iodoform 797
14. Chlorine Preparations 799
15. The Antiseptic Dyes 800
II. Antiseptics Used Chiefly in Skin Diseases 802
1. Pyrogallol 802
2. Chrysarobin 803
3. Naphthol 804
4. Resorcin 805
5. Tar 805
6. Sulfur and Sulfur-containing Compounds 806
7. Balsams 807
III. Genito-urinary Antiseptics 807
1. Hexamethylenetetramine, Methenamine, Hexamine . . 808
2. Mandelic Acid 809

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IV. Disinfectants for Rooms, Furniture, etc. 810
1. Formaldehyde 810
2. Sulfur Dioxide 811
3. Chlorine and Bromine 812
4. Other Disinfectants 813
5. Insecticides 814

PART VI

VACCINES, SERA AND MISCELLANEOUS BIOLOGICALS

1. Vaccines, Toxins and Toxoids 815
2. Antitoxic Sera, Immune Sera, and Antitoxins 818
3. Normal Human Blood Derivatives 820
4. Protein Hydrolysates 821
5. Diagnostic Agents 821
6. Vegetable Toxalbumins: Ricin 822

CLASSIFICATION OF DRUGS ACCORDING TO THEIR THERAPEUTIC USES 824

INDEX 830

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A TEXT-BOOK OF PHARMACOLOGY

INTRODUCTION

Pharmacology is the study of the changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods. Many of the best known of these substances are used to counteract the effects of disease, or to reinforce the tissues in their struggle to maintain their functions, when these are rendered abnormal. These substances are known as **drugs**, and the art of applying drugs in disease is termed **Therapeutics**. Other substances may be of no value in disease, but are of importance because they act as **poisons**, that is, cause dangerous or fatal symptoms in man or animals when they are ingested in quantity. The practical study of the effects of these poisons in man—the diagnosis and the treatment of poisoning, and the methods of detecting the poison—is termed **Toxicology.** But the description and explanation of the symptoms induced by chemical substances belong to the field of pharmacology, whether these substances be drugs or poisons. It is indeed impossible to distinguish between drugs and poisons. Most remedies given in excess cause toxic symptoms, while many poisons are valuable remedies in small doses. Further the actions of many substances are investigated which may never come to be used medicinally as "drugs" but such investigation forms an essential part of pharmacology.

Active agents are formed within the body but the study of them belongs in the first place to the domain of physiology, so long at least as they are not introduced from without. Here no distinct borderline exists between physiology and pharmacology but the scope of their territories may be illustrated by the position of a substance like epinephrine. Epinephrine is a hormone manufactured by the suprarenal gland and the effects produced by this internal formation of epinephrine constitute a part of physiology, a science which deals with the life of the normal organism. Epinephrine may, however, be artificially prepared or synthesized and administered medicinally in doses which may produce concentrations in the blood different from those which occur normally in the body. So used, it becomes a "drug." Conversely, acetylcholine was first studied as a pharmacological agent but has later become of physiological importance from its occurrence and activities in the body. It is especially true of the hormones and of various salts that occur in the body that they come under the domains both of physiology and of pharmacology and the relative importance of a substance to one or other of these sciences may alter with advance in knowledge.

Pharmacology is related equally closely to biochemistry. Thus the part played by vitamins in the normal economy of the organism can be regarded as the immediate concern of biochemistry as that science is now

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usually defined. On the other hand, cod-liver oil had appeared in our pharmacopeias as a "drug," before its value as a source of vitamins was discovered, and now other preparations containing vitamins appear in pharmacopeias or "official lists of medicines." Some brief account of vitamins is therefore, usually included in books on pharmacology.

Similarly the borderline between pathology and pharmacology is sometimes indistinct. Pharmacology may be regarded as the study of the organism rendered abnormal by drugs, while pathology is the study of the organism rendered abnormal by disease. Many of the features of disease are now recognized to be due to the presence of unorganized poisons formed in or by the tissues, poisons which may be allied to, or even identical with, substances used as drugs. Indeed, a substance like histamine may be regarded, under different conditions, as a physiological, pharmacological, or pathological agent. The study of bacteria and of the toxins produced by them belongs primarily to bacteriology. Bacterial toxins are however, related to vegetable toxins, such as ricin, which is obtained from the seeds of *Ricinus communis*, which have long appeared in pharmacopeias. Now that vaccines and antitoxins have found a place in pharmacopeias as remedial agents, some brief reference to them is of convenience in a book on Pharmacology so that the student may have all official remedies simultaneously under review.

Pharmacology is in fact really a department of biology very closely related to other sciences which may be included by that term. It is neither possible nor advisable that the boundaries of these allied sciences should be too strictly limited. Consequently, though in the great majority of cases there need be little hesitation in deciding whether or not a substance is a "drug" and should therefore come under the scope of pharmacology, there is unavoidably some overlapping, and some account must here be given of remedial agents which would not be regarded as "drugs" in the ordinary sense.

The great interest of pharmacology does not lie in its purely biological aspects, however, but in its relation to the treatment of disease. As long as we are ignorant of how a remedy acts in any disease, the treatment is purely empirical; when the mode of action is understood, much greater accuracy can be attained in the treatment. The object of pharmacology is to provide a scientific foundation for therapeutics and to increase the resources of the art of healing. The exact way in which a drug changes the diseased condition can often be followed only imperfectly in man, and recourse must be had to experiments on healthy or diseased animals to elucidate the principles on which it should be employed. In addition, the experimental investigation of new chemical bodies has very frequently demonstrated properties which are of therapeutic value; almost all the new drugs introduced in the last half-century have found their way to the wards through the experimental laboratories.

Pharmacology is one of the most recent developments of medical and biological science. It is true that from the earliest times attempts have been made to explain the effects of drugs on the then prevailing theories of pathology, but the objective study of the action of drugs on

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the organism has been almost entirely developed since the middle of the nineteenth century. The study of drugs was termed **Materia Medica** up to this time, and comprised an examination of their botanical and chemical properties along with some account of the diseases in which they had proved of value. This descriptive rather than experimental study has been continued under the name of **Pharmacognosy**, but is now pursued chiefly by pharmacists. Undoubtedly the student of medicine ought to know those characters of drugs which are of importance in modifying their action and application, but it is undesirable that his valuable time should be occupied in the detailed description of crude substances, which he may probably never have an opportunity of seeing in his future practice.

Another subject which now occupies a much less prominent position in medical study than formerly is **Pharmacy**, or the art of preparing drugs for therapeutic use. Some general knowledge of the methods used is no doubt indispensable to the educated physician, if mainly as an aid to prescribing; but the details may be left to the pharmacist. With the decay of the complex prescription the study of pharmacy by medical students has become less imperative. The relations of medicine to pharmacy have greatly changed in recent years. The physician is dependent upon the manufacturer for his supply of drugs. Many manufacturers now not only make drugs of established reputation but seek to discover new remedies, for which purpose they may have both chemical and pharmacological laboratories at their disposal. A commercial firm not unnaturally endeavors to recoup itself for the expenses of preliminary unproductive research by the profits on the sale of a new drug, which is frequently registered under a proprietary name. The physician is nowadays liable to be overwhelmed by such new remedies, some of which are new only in name and others only slight variants of known drugs. On the other hand, many valuable drugs have been introduced in this way. The physician must endeavor to assess the value of therapeutic claims and should make it a rule not to prescribe substances or preparations of the composition of which he is ignorant. Modern progress in therapeutics has brought other changes in its train. Many alkaloids and synthetic compounds are now distributed in forms which require no manipulation by the retail pharmacist. The practice of giving remedies by injection is becoming increasingly common, often necessitating that the preparations be put up by the manufacturer in ampules which require no further "dispensing." This has led to a decline of individual prescribing and dispensing. This change is perhaps inevitable but will have less serious consequences so long as the preparation which the practitioner prescribes is to him not merely a name but something with whose composition and properties he is adequately conversant.

METHOD OF ACTION OF DRUGS

Stimulation, Depression, Irritation.—When a cell is affected by a poison, the extent of its activity is changed but not the kind. In other words, the effects of drugs are quantitative, not qualitative; the activity of

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living matter may be changed, but the form which the activity assumes is unchangeable.

Drugs which increase the activity of any organ or function are said to *stimulate* it, while those which lessen the activity are said to *depress* it. Another condition induced by drugs is *irritation*, for although this term is often applied loosely as a synonym for stimulation, the two conditions are not identical. Stimulation is properly used to indicate an increase in the specialized function of a cell, producing, for instance, in the spinal cord an increase in the reflex excitability. Irritation, on the other hand, is used rather in reference to the changes in the conditions common to all forms of living matter, that is, it indicates a change in the nutrition and growth of the cell, rather than in the specialized functions. Irritation may thus be induced in all kinds of tissues and is the commonest change caused by drugs in the less differentiated forms, such as the connective tissues and ordinary epithelia; while stimulation is met with in the more highly specialized cells, such as those of the heart, nervous system, or secretory glands. In many instances the irritant action of drugs may be explained by their known reactions with the proteins of the cell; for example, substances which dissolve proteins, or precipitate them, or withdraw fluid from them, all tend to cause irritation when they are applied to living tissues. In other cases irritation appears to be induced through some action the nature of which is quite unknown.

When stimulation is prolonged or excessive, the protoplasm generally becomes depressed and finally loses its activity entirely (paralysis). Some authorities have asserted that depression is invariably preceded by stimulation, and that stimulation sufficiently prolonged invariably leads to depression and paralysis. Both statements are too absolute, although they are true in the great majority of cases. For example, the action of atropine on the terminations of the cardiac inhibitory nerves is purely depressant. Even the most minute quantities of this alkaloid never increase the activity of these terminations, for a quantity too small to weaken them has apparently no effects whatever, and as the dose is increased, the first effect is depression.

Depression, whether induced directly, or following on stimulation, has been shown in several instances to resemble the fatigue induced by the prolonged exercise of the normal organ, and it is probably true that depression and fatigue are, sometimes, identical in appearance, although not necessarily identical in cause. For example, the phenomena of fatigue of the terminations of the motor nerves in muscle resemble those induced by curare, but the fatigued terminations rapidly recover while the curarized recover only when the poison is eliminated.

In most cases an excessive dose of a stimulating poison leads to depression and paralysis. The cell becomes functionally dead, but if the failure of its function does not involve the death of the organism, it may recover and reassume its ordinary function as if no stage of inactivity had intervened. Excessive irritation, on the other hand, leads to actual death and disintegration, from which there is no recovery. For example, the cells of the spinal cord are first stimulated and later

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paralyzed by a large dose of strychnine, but this is not fatal to cold-blooded animals, and after a few days the spinal cord regains its normal function, as the poison is eliminated. On the other hand, the injection of an irritant into the subcutaneous tissues causes structural changes. If only a small quantity be injected, this condition is recovered from, although it generally leaves evidence of its presence in the form of an increase in the fibrous tissue. But if the irritation be intense, the cells undergo degeneration and die, and an abscess is formed. The cells thus destroyed can never recover as the paralyzed ones do. They are either absorbed, or removed by the opening of the abscess, and their room is filled by the overgrowth of the neighboring tissues.

When the effects of a drug are only temporary and the tissue returns to its normal activity when the drug is eliminated, the action is said to be *reversible;* this is the case for most forms of stimulation and depression and for mild irritation. When the cells do not recover but have to be replaced by new growth, the action is *irreversible.*

Distribution and Concentration.—The distribution of a drug in the different tissues and organs of the body must influence its action; and it might be expected that those organs which contain it in largest proportions would show greater changes than others in which it is present in smaller amounts. But this is found not to be true in many instances; for example, the liver often contains larger quantities of alkaloids than any other tissue, yet no symptoms may arise from this organ. The relative concentration in which a drug is present in the different tissues thus does not determine the extent to which these are involved in the action. But if an organ reacts to a drug, the degree of its reaction depends on the concentration in which the drug is presented to it, and the problem in therapeutics is very generally to bring up the concentration in one organ to the efficient threshold without involving other organs; for example, in chloroform anesthesia the object is to cause sufficient concentration in the brain and spinal cord without involving the heart and respiration.

The concentration of a drug in a cell depends in the first instance on the concentration in which it is present in the surrounding fluids and in many cases there seems to be no greater concentration than is in accord with diffusion, the drug being present in the cell in the same concentration as in the fluid. In other instances the drug is deposited in the cell in some form of combination, chemical or physical, and the diffusion continues until the cell may contain the whole of the drug and the surrounding fluid is free from it. As the drug is accumulated in the cell it may finally reach a strength that provokes reaction, but in some instances the drug accumulates in large amount without interfering with the functions of the cell.

The concentration of a drug in the tissues depends primarily on the dose given, but this is modified by the rate of absorption and the rate at which the body frees itself from the drug by excreting it, or changing it into harmless forms. Small divided doses of a remedy may thus never cause the same symptoms as the administration of the same amount undivided. The most striking instance of this is offered in

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anesthesia, for during an operation of an hour's duration much larger amounts of chloroform or ether are taken into the tissues than would be fatal if inhaled more rapidly; the fatal concentration is not reached because excretion is going on at the same time as absorption.

Elective Affinity of Drugs. Protoplasm Poisons.—Most drugs have an elective affinity for certain definite tissues. Thus, some attack the heart only, others the central nervous system and others the terminations of the motor nerves in muscle. Among the cardiac poisons again, some act on the ventricle, others on the auricle, and among the poisons of the central nervous system, some act primarily on the cortex, others on the medulla oblongata and others on the spinal cord. This elective affinity is not merely a question of degree, as is sometimes stated, for a drug which has a powerful action on the brain may have no effect on the heart except when administered in such quantities as alter the physical characters of the blood. A drug may even alter different structures in diametrically opposite directions. Thus, atropine depresses certain nerve terminations, but stimulates the brain; curare, which paralyzes the peripheral terminations of the motor nerves, stimulates the spinal cord. In some instances the immunity of a cell to the action of a drug may perhaps be explained by the latter failing to penetrate into its interior, but this is not true in all cases.

The fields of activity of different drugs vary greatly in extent. One may comprise only the terminations of the secretory fibers in the sweat glands (agaricin), while another, which affects these in the same way, may involve many other terminations in its action (atropine). Most poisons, however, while acting on a certain narrow area in small doses, extend the limits of their activity when larger quantities are ingested. Thus, a poison which acts in small doses on the medulla oblongata only, may, when exhibited in larger quantities, involve the spinal cord and the brain, and in still greater concentration may affect the heart and other organs. No poison is known that acts equally on all organs and tissues, but those which have a wide field of operation are often known as *protoplasmic poisons*. These paralyze any form of living matter when they are brought in contact with it in sufficient quantity, but if they are injected into the blood and thus distributed equally throughout the body, they invariably select some special organs as the chief seat of their activity.

Local, General and Remote Actions.—The *local* action of a drug is that induced at the point of application before it enters the circulation, the *general* or systemic action is that due to its elective affinity for certain organs to which it is carried by the blood. The local effects are very often entirely different in nature from the general action, for a drug may act as an irritant at the point of application and as a depressant to the brain when it is carried to it in the blood. Local effects may be induced wherever the drug can be applied—to the skin, the alimentary tract, the respiratory passages, and the other mucous membranes. They also occur in the subcutaneous tissues when the poison is injected hypodermically, and in any of the deeper organs and tissues which can

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be reached by the needle of the syringe. Local remedies may cause irritation, or may protect the surface from irritation, may depress the sensory end-organs and cause local anesthesia, or lessen secretion, or alter the functions at the point of application in many other ways. They may also have remote effects, as will be mentioned. Many drugs have only a local action, because they are not absorbed, are absorbed in inactive forms, or are excreted or deposited as rapidly as they pass into the circulation, so that enough is not present in the blood at any one time to induce general effects. On the other hand, many powerful poisons have little or no effect at the point of application, but possess an elective affinity only for some organ to which they are carried by the circulation.

Drugs change directly only those organs and tissues with which they come into immediate contact. But the alteration of one part of the organism very often entails that of another to which the drug may not have access, or for which it has no special affinity, because impulses are transmitted through the nerves, or changes are induced in the circulation and nutrition. Thus irritation of the skin may alter the rate of the pulse by impressions being transmitted by the cutaneous nerves and reflected along the inhibitory nerves of the heart. Similarly a poison that weakens the heart may induce disorder of the respiration, from the circulation being deficient in the medulla oblongata; and depression of the brain may lessen the oxidation in the muscles, because it leads to lessened movements. These secondary changes, which are not due to the direct action of the drugs on the organs concerned, are known as *remote* or *indirect* effects.

General Theories of Pharmacological Action.—A number of drugs affect the organism only through their obvious *physical* properties, as when an inert oily body is applied to an abraded surface and promotes its healing by protecting it from irritation and from the evaporation of fluid, or when common salt absorbed into the blood changes its osmotic tension, and thus alters the distribution of fluids in the tissues. On the other hand, many effects are due to simple *chemical* reactions; for instance, bicarbonate of sodium may be used to neutralize the hydrochloric acid of the gastric juice, just as it combines with acid in a test-tube, and many of the effects of oxalates arise from their forming insoluble salts with the calcium of the tissues. In the great majority of drug effects, however, no such simple relations as these obtain and the mode of action remains unknown. This ignorance is not surprising when one considers the extreme complexity of even the simplest living cell and also the complex structure of many drugs.

From the present state of knowledge it can only be said that the activity of drugs depends on a large variety of factors and that pharmacological action cannot be brought under any one law either chemical or physical. In many cases it would appear that the action of drugs is due to their absorption on the cell membrane. In other instances the drug must enter the cell in order to induce its effects. The complex reactions which take place in the cell are made possible by a variety of

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enzyme systems. These are easily affected in the presence of drugs which by combining with the substrate or with essential groupings of the enzyme systems can modify the normal activity of the cell.

The simplest possible conception of the action of most potent drugs is that they unite with certain specific receptors in or on the surface of the cells. The action of a drug on any cell involves at least two separate processes, namely a chemical reaction and the biological response to this reaction. The time relations of these two processes vary in the case of different drug actions. It must also be remembered that a drug may produce a powerful action without exerting any direct effect on the cell in the ordinary sense. For example, many if not all of the actions of physostigmine can be explained by its inhibiting the esterase which destroys acetylcholine in the tissues.

Chemical Constitution and Pharmacological Action.— In 1868 Crum Brown and Fraser published their classical paper on the relation between chemical constitution and pharmacological action and since then continuous attempts have been made to develop and extend their original conceptions. It was supposed that, if the action of a drug is due to a chemical combination between it and the tissues, substances of a similar chemical structure would have similar physiological actions, and in this event the action of a drug might to some extent be foretold from a consideration of its structural formula, provided that the action of similar compounds was already known. For example, methyl, ethyl and propyl alcohols resemble one another closely in their physiological actions, and it might be predicted that butyl and amyl alcohols would act similarly. In point of fact they do, and the pharmacological action of this series of alcohols is, so far, apparently related to their chemical composition. Moreover when the toxicity of this series of alcohols was carefully investigated, it was found that there is a progressive increase in acute toxicity as one proceeds from the lowest to the highest member of the series. It might be predicted, therefore, that alcohols higher than amyl alcohol might be progressively more toxic, but as a matter of experience these proved to be harmless because they became insoluble in the fluids of the body. This result is typical of one way in which the attempt to correlate physiological action and chemical constitution breaks down in detail, because an alteration in the physical properties of a substance may entirely alter its physiological action, though its type of chemical structure remains the same. Resemblances in action may in fact, depend upon some physical property which is common to a group and which has a more immediate bearing on their action than the actual structure; and wherever an attempt is made to follow the relationship between chemical composition and pharmacological action in detail, the analogy may break down because factors which it is impossible to deduce from the chemical structure or formulæ, intrude themselves. Also, side actions which do not admit at present of chemical explanation, may appear in one member of a chemical group and be absent in another. For example, methyl alcohol, though less poisonous from the point of view of minimum lethal dose than ethyl alcohol, has a highly toxic action on the optic nerve which is not displayed by ethyl alcohol.

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Though it is impossible in the present state of knowedge to determine with any certainty the pharmacological action of a drug from a mere consideration of its chemical structure, yet in many cases it is found that substances of closely related structure do exert similar pharmacological actions, and this fact is of great importance in the discovery of new drugs. For example, the discovery of the exact chemical structure of epinephrine led to the synthesis and pharmacological investigation of a large number of related compounds, many of which resemble epinephrine in action, and general conclusions could be drawn as to the type of compound which is likely to exert an action similar to epinephrine.

An interesting branch of this problem has been the investigation of optically isomeric substances. It was found, for example, that l-hyoscyamine is twice as powerful as dl-hyoscyamine (atropine) and that the levo compound is twelve to twenty times as active as the dextro compound. Optical rotation in this case, and in most cases, markedly affects physiological action. Usually but not always, the levo compound is the more active of the two. In such directions important advances have been made in correlating structure and action, and possibly such advances may lead further with the growth of biochemical knowledge.

Pharmacological Syndromes.—Claude Bernard showed that the motor paralysis produced by curare is due to an action on the nerve ends in voluntary muscle and that this action is exerted on all voluntary muscles in a manner qualitatively alike. This discovery suggested—what was not a self-evident truth—that a drug which acted on the nerve ends in one voluntary muscle would act similarly on the nerve ends in all other voluntary muscles. On the assumption that curare acts upon some specific chemical receptor, it follows that there is a chemical uniformity in all such nerve ends and that they all possess the specific chemical receptor upon which curare acts. Subsequent research has extended the value of this conception. Thus a great variety of effects may be produced by epinephrine, all of which are identical to those induced by stimulating sympathetic nerve ends, and the fact that epinephrine mimics all sympathetic nerves is hardly explicable upon any other hypothesis than upon the existence of some common chemical factor in sympathetic terminations in different organs. Such a group of pharmacological actions which are subserved by a common type of physiological mechanism and may be presumed to be due to a common chemical reaction between the drug and the tissues may be regarded as a "homogenous syndrome," however varied the resulting biological responses may be.

Just as a clinical syndrome consists of a group of manifestations induced by a single etiologic agent, so a pharmacological syndrome implies that the multiple reactions to a given drug are explicable on the basis of a single underlying mechanism. Where the reactions to a drug follow a fixed pattern which cannot be explained on the basis of a common type of physiological mechanism, these are designated as a heterogeneous syndrome. In this case it is assumed that a common reaction is present in the diverse physiological systems affected by the drug. The effects induced by acetylcholine is an example of a heterogeneous pharma-

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cological syndrome. This conception of heterogeneous syndromes has a two-fold provocative value. From the point of biochemistry it suggests that, in spite of the differences—structural, functional and chemical—between different tissues, a particular receptor may nevertheless occur in different tissues and that substances, whether chemically related or not, which happen to combine with this receptor will produce the same group of pharmacological effects. From the point of pharmacology it is of value in facilitating investigation, for the discovery of a particular action on one organ may prompt the search for a whole group of actions.

Chemotherapy.—This term has become associated with the specific treatment of infections by artificial remedies. Specific remedies, for example quinine in malaria, have been known for centuries. When the parasitic origin of this disease was discovered, the remedial action of quinine was ascribed to its toxic action on the malarial parasite, whereby the actual cause of the disease was destroyed.

The parasite in question is a protozoal organism, which at one stage of its history inhabits the blood of man and gives rise to the symptoms of malaria. When quinine is given in malaria, the alkaloid circulates in the blood and tissues, all of which, including the parasite, are equally exposed to the action of quinine. For quinine to be a practical remedy it was necessary for it to exert a more powerful action on the parasite than, for example, on the white blood corpuscles; otherwise they would be killed by the same concentration of quinine. It was also necessary that a toxic action on the parasite should be exerted by a concentration of quinine insufficient to damage seriously any tissue of the patient. Quinine fulfils this condition sufficiently well for it to be of practical use, though it is not an ideal remedy because it may produce undesirable symptoms in man when given in a dose sufficient to be effective in killing off the malarial organism. Cinchona bark contains a large number of alkaloids, more or less closely related in chemical constitution to quinine. These other alkaloids have also been tried in malaria to see whether they were superior to quinine for this purpose.

This is one type of chemotherapeutic investigation, the deliberate search for a remedy for an infection from a group of nearly related chemical compounds one of which is known to have a specific action in the disease in question. It would seem that the word "specific" as applied to therapeutic agents has come to acquire vaguely a double meaning. The remedy is specific in the sense that it has a more powerful action on the parasite than on the tissues of the host; it is frequently also specific in the sense that usually a remedy has a much more powerful action on one particular pathogenic organism than on other, often nearly related, parasites.

Not only a great impetus but a new orientation was given to investigation of this kind by the genius of Ehrlich, of whose brilliant work in this connection only a brief account of one example can be given here. It was known that many diseases in man and lower animals were due to infection by organisms of the type of trypanosomes. It had also been discovered that an organic compound of arsenic, atoxyl, had some curative action in diseases of this type. But atoxyl, in the doses required

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to exert a curative action, was very poisonous, often producing serious effects, such as blindness. Ehrlich prepared and investigated a whole series of organic arsenical compounds with a view to discovering one which would be more curative and less poisonous than atoxyl—one which would be, in his nomenclature, more parasitotropic and less organotropic. Eventually he discovered one, 606, also known as salvarsan and arsphenamine, which proved to be superior, as a remedy for syphilis, to any remedy previously available. It was also curative in some allied diseases but it was of little value in sleeping-sickness. The quest has gone on since Ehrlich's early work, for arsenical compounds which should be less toxic even than arsphenamine and which should be more efficacious than arsphenamine in some forms of trypanosomiasis. Thus new compounds have been introduced, and there is every reason to suppose that further improvements in therapeutics will continue to result from this alliance between synthetic chemistry and experimental pharmacology.

Two factors, especially, are necessary for chemotherapeutic investigation. The first is directed chemical research, whereby new compounds modified in certain directions can be made available for pharmacological investigation. The second is the production of a disease in the lower animals. If, as is the case with trypanosomes, a disease can be reproduced in small animals like rats and mice, a large number of controlled experiments can rapidly be carried out. Thus a preliminary knowledge can be acquired as to whether the drug is likely to have a curative action in a particular infection, as to what are its toxic or undesirable actions and what would be an approximate dosage. The final test of its value in a corresponding disease in man must be done on man himself.

The original conception of the value of a specific remedy being based upon a ratio between its toxicity for a pathogenic organism and its toxicity for the tissues of the host, has required considerable modification in the light of later investigations. It has been found for example, that a drug which is curative in a disease due to a particular parasite may have no obvious action on this parasite *in vitro*. Moreover while it may cure one species of animal infected with a particular parasite, it may fail to cure another species infected with the same parasite. For these and other reasons, some of which will be mentioned in the section on organic arsenic compounds, it has become abundantly manifest that coöperation of the tissues of the host plays an important part in the curative action of most, if not all, specific remedies.

CONDITIONS MODIFYING THE EFFECTS OF DRUGS

Biological Variation.—Individuals show marked variability in their reaction to a given stimulus. This biological variation is also manifested in their reaction to drugs. Some individuals will be highly sensitive to the drug; others resistant to its action. A given dose of a drug which will induce a given reaction in the majority of individuals will thus induce a more striking action in a few more sensitive individuals and fail to act in a few who are resistant. The same principle is applicable

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in the case of a poison. If one plots the percentage of individuals succumbing to a given dose of a lethal drug as ordinates, against the dose of the drug used, as abscissæ, one obtains an S-shaped curve as in Fig. 1. In designating the lethal action of a drug, it is thus desirable

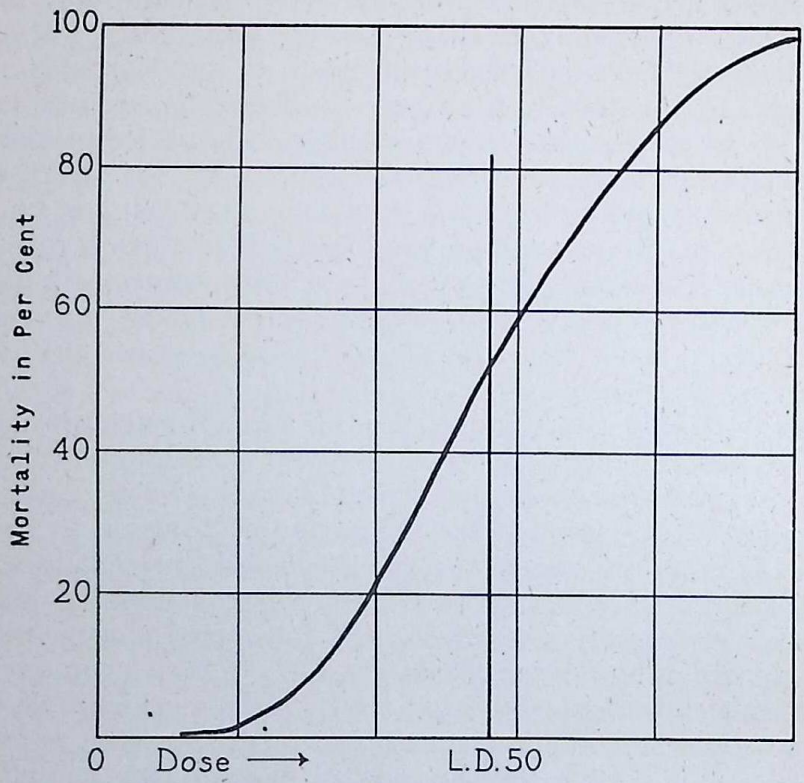

FIG. 1.—A typical S-shaped curve showing the variation in per cent mortality (plotted as ordinates) of groups of frogs injected with varying dilutions of a digitalis extract (plotted as abscissæ). The vertical line at *L.D.50* is drawn to intersect the curve at 50 on the ordinate. The point of intersection of this line with the abscissæ gives the dose which is designated as the *L.D.50* or the dose which is lethal for 50 per cent of the test animals.

to determine the amount of drug which will kill 50 per cent of the animals (the mean *L.D.50*) rather than to try to fix a so-called lethal dose. Likewise by the dose of a drug which is used therapeutically we refer to the average amount of drug necessary in the majority of individuals. This dose will require modification if it is desired to obtain the optimal response from those who require more or less of the drug.

Among the obvious variables which determine the dose required to elicit a given effect are the **size and weight** of the individual. If the same amount of a poison be distributed through the tissues of a large individual as of a small one, the concentration is lower in the organs of the former and less effect is therefore observed. This has been ascertained chiefly in animal experiment, in which the effects of drugs can be estimated much more exactly than in man, but it undoubtedly holds good for human beings also. Very large individuals, then, require a somewhat larger dose than ordinary persons, while in treating individuals of small stature, the dose has to be reduced. For this reason the dosage of many drugs is expressed per unit of body weight when greater accuracy of dosage is necessary.

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Age.—The age of the patient has also to be taken into account in prescribing. Children ought to receive much smaller doses than adults. The more powerful action of drugs in children is due mainly to their smaller size, in part to the more active growth of certain tissues and to the less complete development of others, such as the central nervous system. The dose for a child is generally calculated according to Young's formula, in which a fraction obtained by dividing the age by the (age + 12), is taken as the proportion of the adult dose required; thus, for a child of four years, the dose would be $\frac{4}{4+12}$ or $\frac{1}{4}$ of the adult dose; or more simply according to Dilling's formula, in which the fraction of the adult dose is $\frac{\text{age}}{20}$.

Neither Young's formula nor any of the others which have been devised in its stead is to be regarded as more than a very general approximation, to which there are many exceptions. For example, the narcotics, particularly opium and its preparations, must be given during the first year of life in much smaller quantities than are indicated by Young's rule, while alcohol may be administered in comparatively large doses.

The usual dose advised may be taken as that suitable for an adult of twenty to sixty years. After this age is passed, it is again reduced somewhat. There are exceptions to this rule also, large doses of the purgatives, for example, being often necessary in old people.

Sex.—Women generally require somewhat smaller doses than men, because of their smaller size. It is often stated that their tissues also react more strongly to drugs, but this is certainly not a general rule.

Temporary conditions also influence the activity of drugs. Thus, *after a meal,* a drug is absorbed more slowly than when it is taken fasting, and any local irritant action is also less marked, because the drug is diluted by the contents of the stomach. *Affections of the stomach and intestine* may also modify the effects of drugs; little absorption occurs in the stomach except of drugs that are soluble in oils and lipids, and if the movement of the stomach is lessened or any spasm of the pylorus is present, they may reach the absorbing mucous membrane of the bowel more slowly and thus their effects are retarded or slight; irritant drugs naturally cause more disturbance of the stomach in these cases. Vomiting and diarrhea, of course, tend to lessen the action of drugs by removing them rapidly from the alimentary canal.

During *pregnancy,* purgatives have to be used with great care, because they may induce congestion of the pelvis, and lead to miscarriage. Drugs acting on the uterus, or inducing a marked fall of blood-pressure, are to be avoided because the former may cause the evacuation of the uterine contents, while the latter may lead to asphyxia of the fetus. Many drugs pass from the mother to the child, and this is to be borne in mind, as quantities which are insufficient to poison the former may have more serious effects on the latter. During *lactation,* it is important to remember that active bodies may be excreted in the milk, and may either act on the child or render the milk distasteful to it. During *menstruation,* purgatives are to be avoided, as they tend to increase the flow.

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The **Time of Administration** has also some influence on the effects of drugs. The body is generally more resistant in the morning than in the evening, especially in the case of narcotic drugs; thus a dose of a soporific which may have little or no effect in the early hours, induces sound sleep when given in the evening, partly because the brain is already fatigued and depressed, but also because the action of the drug coincides with the normal time for sleep.

Idiosyncrasy is used to denote an unusual or peculiar reaction to a drug. Some persons react more readily than usual to the ordinary dose, while in other instances a much larger quantity can be taken without any effect. Others, again, show symptoms which are entirely different from and which may, in fact, be diametrically opposed to those ordinarily observed. These idiosyncrasies are naturally more frequently seen and are better known, when they arise from widely used drugs. Thus the modern antipyretics have so often induced abnormal symptoms that these are well known, but it is not improbable that if other drugs had been used, or rather abused, to the same extent, they would be found to induce unusual reactions in an equally large number of individuals. The agranulocytosis which sometimes follows the administration of a variety of drugs (aminopyrine, sulfonamides, gold salts, *etc.*) is an example of idiosyncrasy.

The failure of the individual to react to the ordinary dose of a drug is known as **Tolerance**, and this particular form of idiosyncrasy may be termed *congenital* tolerance. Certain species of animals tolerate quantities of drugs which would be fatal to others of the same size. In fact, so frequently is this the case that it is impossible to determine the fatal dose of any drug on an animal from experiments performed upon others of a different species, even though it be nearly related. One of the most remarkable examples of this form of tolerance is met with in the hedgehog, which resists large doses of many very active poisons. Another well-known example is the tolerance of the rabbit to large quantities of atropine.

A form of tolerance which is a matter of everyday observation is that induced by the prolonged use of a drug, which has been called *acquired* tolerance, or mithridatism, from the tradition that Mithridates protected himself in this way from the danger of poisoning. The most familiar example of this form of tolerance is that acquired for tobacco (nicotine); the first cigar often induces violent poisoning, but if a habit be formed, considerable amounts of nicotine may be absorbed without apparent harm, because the tissues become accustomed to the presence of small quantities of nicotine, and thus fail to react to it. This tolerance is entirely different from the immunity induced by toxins (see Toxins), and it is desirable that the two terms should be kept distinct.

An important form of tolerance is the resistance developed by trypanosomes and other pathogenic organisms for certain drugs. Thus by subjecting susceptible organisms to inadequate doses of a drug it is possible to render them "drug fast," that is, resistant to the drug even when used in what would originally have been an adequate dosage. This form of tolerance can be acquired by organisms cultivated *in vitro* as well as *in vivo*.

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Very often while some tissues acquire tolerance for a poison, others fail to do so, and either react in the same way as before or may suffer from the prolonged use of excessive quantities; for example, although after prolonged use morphine loses its action on the brain, so that large doses have to be given to relieve pain, tolerance is less developed in the bowel, so that constipation continues to be induced by smaller amounts; similarly in a dog tolerant to morphine, the cardiac inhibitory center retains its sensitiveness to it. Some animals fail to develop tolerance for certain drugs; for example the rabbit remains sensitive to morphine after prolonged treatment. It is to be noted that tolerance is soon lost if the drug be discontinued for some time. This is of great importance in cases of opium-eating, for a person who has taken opium for a long time acquires a tolerance for the drug, so that sometimes enormous quantities are required in order to induce the ordinary effects; but if the habit be discontinued for some time, the tolerance is lost, and a dose which would formerly have had little effect may now induce dangerous poisoning. The prolonged use of one drug may establish tolerance for others of the same class. Thus chronic drunkards become less sensitive to large quantities of alcohol, and are also more resistant to the action of ether than ordinary persons, this being due to the fact that ether and alcohol act on the same nerve cells in the same direction, and probably induce the same changes in the protoplasm.

In some instances when tolerance is established for a drug, it is found that the tissues destroy more of it than previously (morphine and alcohol), or excrete it more rapidly, as is said to occur under atropine in some animals, or perhaps absorb it less readily (arsenic). The drug thus never reaches the same concentration in the tissues and the absence of action is thus partly explained. In addition to this, however, the organs normally affected become less susceptible to the drug; for though in morphine tolerance much more is destroyed than in normal persons, enough remains in the blood to cause deep narcosis in ordinary people, yet no symptoms are induced in the patient.

The **Cumulative Effect** of drugs is another phenomenon caused by their continued ingestion. Small doses of certain drugs taken repeatedly for some time eventually cause symptoms which are much more marked than those that follow the first dose. This seems due to the accumulation of considerable quantities in the tissues. The absorption may be more rapid than the excretion, and each new dose thus adds to the total quantity in the blood and organs more than is lost in the same time by excretion. The classical example of cumulative action is that of digitalis, but it is much more frequently induced by such drugs as mercury, arsenic, or the iodides, for the so-called chronic poisoning induced by these is really an example of cumulative action. Cumulative action may occur along with tolerance. Thus the tolerance of certain tissues for nicotine does not protect others from the effects of the abuse of tobacco.

Synergists.—The presence of another drug having the same effects in the body often increases the action of a remedy to an unexpected extent. This is the ground for the prescription of several remedies acting in the same way. For example, several purgatives prescribed

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together often act more efficiently than any one given in quantity equal to all of them. This is easily explicable upon the assumption that, although all are alike in their chief features, they differ in the details of their reactions, so that parts of the alimentary canal which might escape one are affected by another, and the mixture thus acts more universally than any one of the components. Other examples of synergism are offered by the narcotics, for it has been shown that a mixture of morphine and chloral, for example, is more efficient than either administered alone in larger dose. Another recent example is offered by the use of mercury and arsenical compounds in syphilis, which act better together than when either is used alone. The importance of synergism is often exaggerated, but in some examples the increased activity of one drug in the presence of another is remarkable.

On the other hand, a drug may fail to elicit any symptoms if an **antagonistic** substance is present in the body. Thus in cases where a powerful nervous depressant, such as chloroform, has been inhaled, strychnine may have little or no effect on the spinal cord in doses which would normally increase the reflexes to a marked extent. In the same way, if the terminations of the inhibitory fibers of the heart are paralyzed by atropine, a poison which normally slows the heart by stimulating these terminations will have no effect in the usual doses.

Similar modifications of the effects of drugs may be induced by poisons formed by pathological changes in the tissues, or by an unusual state of irritation or of depression of the tissues themselves. For example, the excitable uterus of pregnancy may react by contraction to certain drugs which excite both the motor and the inhibitory nerves and which in the more inert non-gravid organ cause relaxation. Similarly, the sulfonamides fail to exert their bacteriostatic action in the presence of pus or necrotic tissue because these contain aminobenzoic acid which inhibits the action of the sulfonamide drugs.

Pathological conditions often modify the effects of drugs to a very considerable extent, and in a way which cannot be explained at present. For example, the antipyretics reduce the temperature in fever, but have no effect on it in health; the bromides lessen the convulsions in epilepsy but have much less effect in depressing the brain in normal persons; epinephrine relaxes the constricted bronchioles of the asthmatic but has little effect on the normal lung. In general, however, although the effect of a drug in a pathological condition may be greatly exaggerated over that observed in the normal, its action is qualitatively the same in both conditions. Thus the analgesic effects of the antipyretics, the sedative effects of the bromides and the sympatheticomimetic action of epinephrine would suggest their usefulness under the pathological conditions cited above. Moreover, in a large number of instances drugs are given, not in order to act upon the diseased tissues, but upon healthy ones. For instance, in diseases of the cardiac valves, drugs are given, not with the object of restoring their integrity, but to act upon the healthy heart muscle, and to obviate the disturbance of the circulation which is caused by the destruction of the valves.

Whenever possible an attempt is made to study the action of drugs

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on diseased tissues or on the disease in animals, as has been done very largely in recent years in various infectious disorders (see Chemotherapy).

METHODS OF ADMINISTRATION

Drugs are applied for their **Local Action** to the skin, to the mucous membranes of the alimentary, respiratory, and genito-urinary tracts, and to the conjunctiva and cornea. Even deeper tissues and organs can be treated locally by the injection of remedies into them. The objects of local medication are very diverse, and can be treated of only in connection with the individual drugs. The methods of application are also so numerous that only a few of the chief can be mentioned. Drugs intended for application to the skin are often formed into salves or ointments (unguenta) by mixing them with oily or fatty substances, which adhere to the skin and do not dry up, and which, in addition to serving as a means of applying an active substance, protect the surface from the air and from irritation. Other preparations for application to the skin, such as the plasters (emplastra), resemble the ointments in their general characters, but also give mechanical support and bind surfaces together from their being spread on paper or cloth, which thus serves as a flexible splint. The collodions and cerates resemble the plasters; the oleates, the ointments. In addition to these special preparations, drugs may be applied to the skin in solutions, or as powders, or solid masses may be used to cauterize it.

The methods of applying drugs to the alimentary tract and to the lungs for their local action are for the most part similar to those used for drugs which are intended to be absorbed. The mouth and throat may be washed out with solutions, which are gargled (gargarismata), or may be treated with powders, or lozenges (trochisci), which are slowly dissolved and thus permit of a more prolonged and constant action in the mouth than is possible if the drug be swallowed immediately. The nose may be washed out with solutions of active drugs, or powders may be drawn into the nostrils as snuffs; the latter often cause sneezing, and are sometimes known as sternutatories, or errhines. The larynx may be treated locally by the application of powders or of very small quantities of fluids by the aid of the laryngoscopic mirror and probe. Solutions are generally used for application to the conjunctiva, but a more permanent effect can often be obtained from ointments, lamellæ, or powders which are less liable to be washed away by the tears. The urethra, vagina and uterus are treated by the injection of solutions, or by ointments and powders. Bougies, which are occasionally advised, are formed by incorporating an active drug in some substance which is solid at ordinary temperatures, but melts when introduced into the organ and allows the drug to come into contact with the surface. The rectum may similarly be treated by the injection of drugs in solution or suspension (enemata), or by the use of suppositories. Drugs are not infrequently applied by the rectum in order to elicit their action after absorption, but much oftener for their local action on the bowel. Enemata may be either large (a pint

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or more) or small (2 to 5 cc.). The large enemata are used either to wash out the intestines, and may then contain an antiseptic or astringent, or to induce peristalsis and evacuation of the bowel, when they are made up of water with or without soap or other slightly irritant substances. The small enemata are used chiefly to induce evacuation, and contain more irritant substances, such as glycerin alone or along with some more active body. Suppositories are usually formed of cacao-butter, which is solid at room temperature, but melts at the temperature of the body.

Drugs whose **General Action** is to be elicited after their absorption are given by the mouth, except when some special character in them or in the disease renders some other method preferable. They may be given by the mouth in solution in water, alcohol, oils, or other more or less indifferent bodies. The disagreeable taste of many remedies, however, often precludes this method, and these may be ordered in the form of pills, or in capsules, which are formed of gelatin or similar substances and are dissolved in the stomach and intestines. Very often the disagreeable taste may be concealed by the addition of sugar, or of some strongly tasting but agreeable body, such as a volatile oil. Insoluble drugs may be given as powders, as they have little or no taste. Powders are also used as a means of administering soluble drugs, if they have not a disagreeable taste and have no marked local action, but very deliquescent drugs should not be given in this form. Insoluble drugs are sometimes ordered in suspension in mucilaginous fluids; and oils, which are distasteful to many people, may be given mixed with water and gums (emulsions).

The rate of absorption from the *alimentary canal* varies greatly with different drugs and also with the form in which they are administered. The first point will be treated of in connection with the individual drugs. As regards the second, it may be stated that drugs are more rapidly absorbed when they are swallowed in solution, and that, when much inert and insoluble matter is associated with them, their absorption is much retarded. This fact is taken advantage of in practice by giving drugs in solution when rapid absorption is desirable, and by giving less pure forms when the local action on the stomach and bowel is to be elicited. The more concentrated the solution, the greater is the irritant action on the stomach, and thus where irritation of the stomach is desired, either the solid drug or a strong solution is given; but as a general rule the local action on the stomach is to be avoided, and drugs are therefore ordered in as dilute solution as is possible without increasing the bulk to too great an extent. It is to be noted that drugs which are insoluble in the test-tube may be rendered soluble by the action of the gastric and intestinal juices, while many which are given in solution are precipitated in the stomach.

Drugs absorbed from the stomach and intestine are carried to the liver before reaching the general circulation, and this is of great importance in determining their effects in the body, as some of them are retained in that organ, and are either entirely destroyed or escape so slowly that they have no perceptible effect.

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Drugs are occasionally introduced into the *rectum* so as to obtain their general action. The local effects on the stomach are thus avoided and some of the drug reaches the circulation without passing through the liver; morphine and opium are sometimes so administered. Drugs are absorbed more slowly from the rectum than from the small intestine but absorption may begin sooner than when a drug is given by mouth, as in the latter case the drug may be delayed in the stomach.

Another important method of administering drugs for their general action and also for their local effects is by inhalation into *the lungs*. Only volatile drugs can be used thus for their general action. They are absorbed very rapidly, owing to the extensive surface to which they are applied, and also because volatile substances penetrate the tissues more readily than others. The best examples of inhalation are offered by the general anesthetics, chloroform and ether. Most substances absorbed by the lungs are also excreted by them, and this leads to an important practical point in regard to the anesthetics. For the passage of gases or vapors through the lining epithelium of the alveoli depends upon their partial pressure, that is, upon their concentration in the air and blood respectively. Accordingly, when the air contains more chloroform vapor than the blood, the anesthetic passes into the blood, but as soon as the condition is reversed, and the blood contains more chloroform than the air of the alveoli, it commences to pass backward. The more concentrated the vapor inhaled, the more chloroform is contained in each cubic centimeter of blood, and the greater is the action on the nervous centers and the heart.

Less volatile substances are sometimes inhaled into the lungs for their local action, and even non-volatile bodies suspended in a spray or vapor may be thrown into the respiratory passages, but it may be questioned whether these last really reach the alveoli except in traces.

Drugs may also be administered by other mucous membranes for their general effects. For example, pituitary extract may be administered by application to the nasal mucous membrane, which is highly vascular and affords a rapidly absorbing surface. Drugs are also rapidly absorbed from the thin mucous membrane underlying the tongue. Nitroglycerin and sometimes certain of the steroid hormones are administered by the sublingual route. It must be remembered that symptoms may arise from the unwanted absorption of a drug which is being used for its local action; even death has occasionally occurred, for example, from the absorption of cocaine from the nose or urethra when it has been applied to these mucous membranes as a local anesthetic. Similarly, drugs applied as dressings to wounds or abrasions have often given rise to severe or fatal poisoning from being absorbed into the blood.

Drugs are also applied to *the skin* in order to elicit their general action. Volatile bodies are certainly absorbed by it, although much more slowly than by the lungs or by the stomach and intestine. Solutions in water of non-volatile drugs are not absorbed from the skin, but solutions of certain remedies in alcohols, oils, fats, ether, and some other substances which are capable of dissolving or mixing with the

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fatty covering of the skin, are absorbed fairly rapidly if they are rubbed in thoroughly. This method of application (inunction) has been used chiefly for the absorption of mercury, as the local action on the stomach and bowel is thus avoided. (See Mercury.) Alkaloids do not appear to be absorbed by the skin even when dissolved in oils or alcohol.

In the *hypodermic method* drugs are injected through a fine hollow needle into the subcutaneous, or, in the case of more irritant substances, into the muscular tissue, where they meet with fewer sensory nerves. Absorption occurs more rapidly than when drugs are given by the mouth, the local action on the alimentary canal is avoided, and the physician is more certain that the whole of the remedy is effective, provided it is soluble and is not precipitated at the point of injection. At the same time, the method has certain drawbacks, the chief of which are the pain of the injection and the danger of injecting a powerful remedy into one of the subcutaneous veins. Hypodermic injections should be made only by the physician or trained attendant. The needle and syringe ought to be sterilized, and the substance injected should be aseptic. As a general rule, solutions in water or in dilute alcohol are used for injection, but the insoluble salts of mercury have also been injected, suspended in oil. (See Mercury.) Irritant drugs are to be avoided as far as possible, as they cause great pain, swelling and sometimes suppuration or sloughing, even when the injection has been carried out aseptically. If there is any doubt as to the irritant action of a drug, the injection should be made into muscle (gluteus) as disastrous results have followed from ignorance of the local action of such remedies as quinine or calcium salts. Ringer's solution should be used instead of plain water when possible. Hypodermic injection is used very largely to elicit the general action of a remedy, but also for the local effects, as when cocaine is injected in order to produce local anesthesia. As the absorption from the subcutaneous tissues is usually more rapid than that from the stomach and intestine, when the drug is in perfect solution, the dose has to be reduced. As a general rule, about one-half of the ordinary amount is sufficient.

Deeper injections are sometimes made for their local action on the organs. Thus, antiseptics have been injected into lung cavities, caustics into tumors, local anesthetics into the spinal canal, and direct applications have been made to the nerves in sciatica and other similar disorders.

In order to maintain a constant absorption of a drug rather than the discontinuous action of repeated injections, the use of pellets of solid insoluble materials implanted in the subcutaneous tissue (*e. g.*, steroid hormones) or relatively insoluble derivatives (*e. g.*, protamine insulin) or drugs in an insoluble menstruum (*e. g.*, penicillin in oil and beeswax) may be administered. In this way the organism is presented with a constant supply of the drug without the necessity of frequent injections.

Intravenous injection is the most certain and rapid method of bringing drugs into the circulation and tissues. A long hypodermic needle is passed directly into one of the superficial veins of the arm and the dissolved drug is slowly injected in quantities of the solution which may

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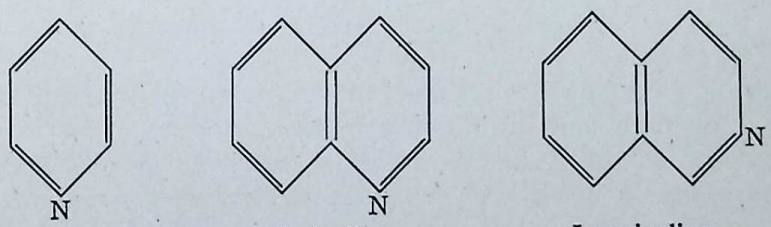
vary from 1 cc. to 200 cc. The drug must be in complete solution and must not react with the protein of the blood; thus strongly acid drugs and dissociable salts of the heavy metals should be avoided; on the other hand, drugs, *e. g.*, the sulfonamides, which are too irritant for hypodermic injection may sometimes be given intravenously. The most perfect asepsis should be aimed at. The dose is usually much smaller than that given by the mouth, but no general rule can be given. The toxicity of a drug by intravenous injection is often greatly reduced by injecting it slowly and well diluted.

The galvanic current has also been employed to aid in securing the penetration of certain drugs into the deeper tissues where they may be taken up by the blood stream and act particularly upon the tissues in the neighborhood of the point of application. In this method, which is known as "iontophoresis" or "common ion transfer," it is possible under proper conditions to secure the action of the drug employed upon the deeper tissues without at the same time bringing about systemic effects, although occasionally symptoms are produced indicating a general action.

THE CHEMICAL CHARACTERS OF DRUGS

Many substances which induce changes in the living organism are comparatively simple chemical compounds. In the inorganic materia medica are found many salts, bases and acids, and a few uncombined elements, such as mercury and sulfur, while organic chemistry offers alcohols, ethers, phenols, ketones and an ever increasing number of more complex synthetic compounds. But some groups of substances which occur widely in plants require some discussion before the individual members are taken up severally.

The first group of these is formed by the **Alkaloids**, which are substituted ammonias, and have a more or less strongly alkaline reaction,



Pyridine **Quinoline** **Isoquinoline**

so that they are often known as the vegetable bases. They contain carbon, hydrogen, nitrogen, and, as a general rule, oxygen, although some of them, such as coniine, are devoid of it. Like ammonia, they combine readily with acids without eliminating hydrogen, and the salts thus formed resemble those of ammonia in many respects, among others in being thrown out of combination by the fixed alkalies. Many vegetable alkaloids are derived from pyridine, quinoline and isoquinoline by the addition of hydrogen, and generally by the substitution of one or more of the hydrogen atoms by side chains of greater or less complexity.

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Some of the vegetable alkaloids have been formed synthetically in the laboratory, and the constitution of some of the others is perfectly well known, but many of them have not yet been isolated, and there are probably others whose existence is not even suspected. These vegetable alkaloids occur in almost all parts of plants, although they are found in greatest abundance in the seeds and roots. The same alkaloid is often found in most of the plants of a genus, or it may occur in one or two species of a genus and in other plants which are in no way related. Very often several alkaloids are found in a plant, and these may differ entirely in their action on animals, although not infrequently all the alkaloids of a plant resemble each other in their effects. The alkaloids are found most abundantly in dicotyledonous plants, but some are obtained from the monocotyledons. Muscarine, ergotoxine and other bases are found in the fungi and alkaloids have been isolated from the suprarenal capsule of animals and from the skin and glands of reptiles.

The alkaloids are very often only slightly soluble in water, but form salts which are generally more soluble. Many of the bases are dissolved by ether, chloroform and amyl alcohol, while the salts are insoluble in these. Both bases and salts are generally fairly soluble in alcohol. The hydroxides and carbonates of the alkalies and the alkaline earths precipitate the alkaloids from solutions of the salts in water, a point of some importance in prescribing these bodies.

Another important class of vegetable poisons is formed by the **Glucosides** (glycosides), which are esters (compound ethers) composed of sugars and hydroxyl substances, and which liberate sugar when they are heated with acids, or sometimes with alkalies, or when certain unorganized ferments act on them. Many of the glycosides contain only carbon, hydrogen and oxygen, a few have nitrogen in addition, and one or two, sulfur. In some instances, the remainder, after the sugar is split off, is an alkaloid, *e. g.*, solanidine. Glycosides differ greatly in their solubility in water and alcohol; comparatively few of them are soluble in ether. Some of the glycosides are powerful poisons, others have little or no action.

Resins, an ill-defined group, are found in many plants, and are characterized by their smooth, shining fracture, and by their insolubility in water and solubility in ether, chloroform, volatile oils, benzol and, in many cases, in alcohol. They seem to be formed in plants by the oxidation of volatile oils, and are often acid or anhydride in character, while others are apparently alcohols or esters. The resins are almost invariably composed of several different substances mixed together.

Oleoresins are solutions of resins in ethereal oils, which lend them a characteristic odor and taste. The term "*Balsam*" is often used as synonymous with oleoresin, but most writers restrict it to those oleoresins which contain benzoic or cinnamic acid along with other constituents. *Gum-resins* are mixtures of resins and gums, generally containing some volatile oils. They are insoluble in water, but the resin is suspended in it by the gum. On the other hand, the resin is dissolved by alcohol, while the gum remains insoluble.

Gums are amorphous, transparent substances, composed of carbo-

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hydrates of the formula $(C_6H_{10}O_5)_n$ and are thus nearly related to cellulose and starch. Some of them are soluble in water, while others merely swell to a jelly in it; they are insoluble in alcohol. They generally occur in plants in combination with calcium, magnesium or potassium; they have no poisonous action, but form a protective covering for irritated surfaces, and are largely used to suspend in water substances which are insoluble in it, such as resins and oils.

Volatile oils (v. p. 207) occur in plants in large numbers.

Fats, oils, sugars, acids, starch, proteins, coloring matter, ferments and other bodies which occur in plants, and are contained in many of the preparations used in therapeutics, are not generally possessed of any action of importance.

The most important drugs introduced into medicine in recent years are the synthetic organic chemicals which include anti-infectives such as quinacrine, the sulfonamides, etc.; local and general anesthetics; antiseptics; the vitamins and hormones, derived either by extraction from natural sources or prepared synthetically; and the antibiotics, derived from molds and bacteria.

THE PHARMACOPEIAS AND PHARMACOPEIAL PREPARATIONS

Almost all governments have found it necessary to regulate the preparation of drugs used in therapeutics, and for this purpose issue at intervals codes of instructions defining the characters of the drugs and giving the exact formulæ according to which they are to be prepared for use. These codes are known as **Pharmacopeias**, and some differences exist between those of different countries, although the most important drugs are found in all of them. All the drugs used in therapeutics are not found in the pharmacopeias, for these are issued only at intervals of several years, and in the meantime valuable remedies may be introduced. The pharmacopeia of the United States is now revised every five years and the twelfth revision was published in 1940. A supplement appeared in 1943. The last edition of the British Pharmacopeia appeared in 1932 but seven addenda to it have been published since 1936. The official definition of therapeutic substances is of advantage to both physician and pharmacist, as it assures the former that the drug he prescribes will have a uniform quality, wherever in the country it is dispensed, while the pharmacist is saved from the continual preparation of remedies in different forms, by their being prescribed in one recognized strength.

Apart from the official pharmacopœias, other lists of drugs and formulæ are published for the guidance of medical practitioners and pharmacists. Thus the American Pharmaceutical Association issues the "National Formulary" (N. F.), a collection of formulæ which is also a legal standard, and the American Medical Association publishes annually "New and Non-official Remedies" (N. N. R.), which contains descriptions of proprietary drugs which are marketed in an acceptable manner. The Council of the Pharmaceutical Society of Great Britain publishes the "British Pharmaceutical Codex" (B. P. C.), with the object of providing recognized formulæ for medicines which are not officially recognized in the British Pharmacopœia.

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The pharmacopeias contain a large number of pure substances such as salts, acids, bases, alkaloids, and these require no further description. On the other hand, many of the drugs are given in an impure form, either because the active principle is unknown, or because its isolation is attended with difficulty and expense. Thus many of the vegetable remedies are presented in the pharmacopeias as solutions or solids which contain not only the active principle but gums, sugars, coloring matter, and many other impurities. These are provided in different forms to allow of variation in their administration. In addition, the pharmacopeias contain a number of official prescriptions, that is, mixtures of active substances in such proportions as are ordinarily prescribed. These are generally designated by the addition of "compound" (compositus) to the name of the chief ingredient.

Many crude or unprepared drugs are found in the pharmacopeias, such as leaves, roots, flowers, or even whole plants. These are used chiefly for the preparation of other more readily applicable remedies, but are sometimes prescribed as powders or in pills.

The following preparations[1] are official:

a. *Aqueous Preparations*

Aquæ, medicated waters, generally contain only traces of some volatile substance, such as an ethereal oil or chloroform, in solution in water, and these are used in prescriptions as more agreeable to the taste and smell than pure water but have little further effect. In the U. S. P. the solutions of ammonia and hydrogen peroxide are also included under aquæ, but these are used only to elicit the specific effects of these drugs. In the B. P. these strong solutions are included in the liquores.

Liquores (U. S. P.) are solutions in water of soluble substances. Many of these are 1 per cent in strength.

Liquores (B. P.) are solutions in the widest sense, in water, alcohol, or other fluids.

Decocta (U. S. P.) or decoctions, are solutions of vegetable principles, which are obtained by boiling parts of plants in water.

Infusa, or infusions, are solutions obtained by soaking parts of plants in water, which may be hot or cold, but is not kept boiling. Infusions and decoctions are weak preparations and tend to decompose rapidly. Many drugs in the B. P. have both a fresh infusion (Infusum Recens) and a concentrated infusion (Infusum Concentratum). The latter diluted with seven times its volume of distilled water yields a product resembling the fresh infusion.

Misturæ, or mixtures, are preparations in which substances insoluble in water are suspended in it by means of gums or similar viscid substances, or are mixtures of solutions.

Emulsa (U. S. P.), emulsions, are formed by suspending oils in water by means of gums or other viscid bodies. The B. P. contains no official emulsions.

Mucilagines, mucilages, are solutions in water of gums, starch, and similar colloid bodies.

Magmas (U. S. P.), or milks, are suspensions of bulky, white insoluble preparations in water.

Syrupi, syrups, are strong solutions of sugar in water, which may be used alone, or may be impregnated with more active bodies. Similar preparations formed with honey instead of syrup (sometimes known as *mellita*) are official, as Mel Boracis (B. P.).

[1] The student is advised to omit the following list for the present, and to refer to it only as he takes up the preparations of the individual drugs. Most of these preparations are found in both pharmacopeias. Those which occur only in the British are indicated by B. P., while those which are confined to the United States are marked U. S. P.

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Lotions (B. P.), lotions, or washes. This term is used to designate a preparation of mercury, the black wash.

b. *Alcoholic Preparations*

Spiritus, spirits, are solutions of volatile bodies in alcohol, and often owe their chief action to the solvent and not to the drug contained in it.

Elixiria, elixirs, are sweetened aromatic preparations containing diluted alcohol or glycerin.

Tincturæ, tinctures, are solutions in alcohol of medicinal substances, which are generally formed from parts of plants by maceration or percolation. They contain both volatile and non-volatile ingredients, but the latter are generally the more important.

Fluidextracta (U. S. P.), *Extracta Liquida* (B. P.), fluidextracts, are prepared from plants by forming solutions in water or more frequently in alcohol, and evaporating them until the solutions contain as many cubic centimeters as the original crude drugs weighed in grams; that is, the volume of the fluid extract corresponds to the weight of the crude drug. When the active principle is assayed, however, the liquid extract is diluted to contain a definite amount of it, and without reference to the quantity of the crude drug used.

The tinctures and fluid extracts are the most commonly used liquid preparations, and most of the important drugs are prepared in one or both of these forms.

c. *Other Fluid Preparations*

Glycerita (U. S. P.) or *Glycerina* (B. P.) are solutions of medicinal substances in glycerin.

Collodia, collodions, are solutions of medicinal substances in collodion, which is itself a solution of pyroxylin in alcohol and ether.

Aceta, or medicated vinegars, are solutions of medicinal substances in vinegar or diluted acetic acid.

Linimenta, liniments, embrocations, are preparations in which active remedies are dissolved or suspended in dilute alcohol, oils, or water. They generally contain an oil or soap and are intended to be applied to the skin.

d. *Solid and Semi-solid Preparations*

Extracta, extracts, are formed from solutions such as tinctures, decoctions, or infusions by evaporation, which is continued until there remains a solid mass. The extracts thus contain all the substances which are taken up by the solvent, except those which are driven off or decomposed at the temperature at which evaporation is carried on.

Pilulæ, pills, are globular masses of small size, such as admits of their being easily swallowed. They are formed from extracts, or from powders, by the addition of some substance to give them the necessary cohesion and consistency. Pills generally weigh 0.1–0.3 gram (2–5 gr.). The U. S. P. determines the composition and size of the official pills, so that the doses can be modified only by ordering several pills to be taken at one time. The B. P. leaves the pills unformed, so that they may be prescribed of any size. The Pilulæ of the B. P. really corresponds not to the Pilulæ, but to the Massæ of the U. S. P.

Massæ (U. S. P.), masses, are preparations made up of the proper consistency for pills. They are invariably prescribed in the form of pills.

Confectiones, confections or electuaries, are soft, solid preparations consisting of sugar or honey impregnated with some more active body.

Suppositoria, or suppositories, are intended for insertion into the rectum, urethra, or vagina, and are, except in one or two cases, formed by mixing the active ingredient with cacao-butter. Suppositories for the rectum are conical in shape and weigh about a gram (15 gr.). Those for the urethra (*bougies*) are of the same weight, but are pencil-shaped, while the vaginal suppositories are globular, and weigh about 3 gram (45 gr.).

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Pulveres, powders, are simply dry substances in a state of fine division. Most of the official powders are mixtures of several active bodies.

Triturationes (U. S. P.), triturations, are formed from powders by diluting them with nine parts of sugar of milk.

Tabellæ, tablets are solid discs prepared by compressing or moulding a drug, or a mixture of drugs.

Trochisci, troches, or lozenges, (B. P.) are solid masses generally of a flattened shape, and consist of powders or other bodies, incorporated in sugar and gum.

Lamellæ (B. P.), or discs, are small discs formed of gelatin with some glycerin, each weighing 1 to 2 mgms. They are impregnated with an active drug, and are applied to the conjunctiva in order to elicit the local effects.

Unguenta, ointments, salves, are soft, oily substances which are applied to the skin by rubbing. (See page 193.)

Oculenta (B. P.) are ointments for the eye.

Cerata (U. S. P.), cerates, resemble ointments, but are rendered harder by the addition of wax. (See page 195.)

Emplastra, (U. S. P.) plasters, are adhesive bodies of a still harder consistency than cerates, and soften only when heated.

Cataplasmata (B. P.), poultices, are soft, pasty preparations for application to the surface of the body. Only one, Cataplasma Kaolini, is official, but many unofficial poultices are in common use.

Unofficial Preparations

Cachets are thin discs of dough of the shape of a soup-plate and varying from ½ in. to 1½ in. in diameter. When two of them are placed together with their concave sides toward each other, they form a receptacle in which powders are dispensed. The edges stick together when they are moistened. A somewhat similar method of dispensing is in gelatin *capsules*, which may be hard or soft, and which are made in different sizes. The hard capsule is used for solids, the soft for liquids. Sometimes the latter contain as much as 15 cc. (½ fl. oz.), but these are difficult to swallow.

Enemata, clysmata, or clysters, are liquid substances injected into the rectum for their local or general effects. (See page 29.)

Pellets are compressed cylinders of crystalline insoluble steroids for subcutaneous implantation.

BIOLOGICAL ASSAY

The accurate use of drugs in therapeutics involves that the amount of active principle given in each dose must be as uniform as possible and not subject to irregular variations. In most cases the strength of a preparation can be determined by ordinary chemical methods, and this is required for most of the more powerful substances used in therapeutics. This cannot be done for certain important drugs, however, because the active constituents are insufficiently known, or when known cannot be isolated quantitatively. This has led to the method of biological assay, in which the strength of a preparation is estimated by its effects on living animals or tissues. Biological assay was first used industrially to determine the strength of the antitoxic sera, and soon afterward Houghton introduced it to regulate the strength of the preparations of the digitalis series, from which it has been extended to several other substances, and it has now received recognition in pharmacopeias.

The principle underlying biological assay is that a definite quantity of a drug will always produce a certain degree of deflection from the

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normal in the same animal or in animals of the same species. The reaction, it is true, is not always identical, for many conditions may alter the extent to which an animal reacts to a drug, and every precaution must be taken to keep the conditions uniform in making these tests. For example, the reaction varies inversely with the weight of the animals, and these must be taken as nearly as possible of the same weight and age or, if this is not possible, the dose must be calculated in terms of the weight of the animal. And when great accuracy is required, the test must be done upon a series of animals sufficiently large to eliminate the variations and idiosyncrasies that cannot be controlled. These tests require special training and laboratory experience and are very time-consuming. The method is not likely to be substituted for chemical assay when the latter is available and adequate. In the case of some drugs, *e. g.*, the organic arsenicals, living tissues can detect differences that are not discovered by available physico-chemical methods and the latter have to be supplemented by biological tests for therapeutic activity and for toxicity. Most preparations requiring biological assay are either preparations from plants, animal organ extracts, or antitoxic sera. Such preparations cannot be tested chemically but yet require to be given in physiologically accurate dosage.

The accuracy and value of biological assay depend upon scrupulous attention to details of procedure and no abbreviated description of a method would enable one to carry out a biological assay. The methods fully described in the pharmacopeias and elsewhere must be consulted. It is only possible here to mention the official preparations which require such standardization and to give some indication of the principles involved.

In biological assay the object is to compare quantitatively the effects of a preparation with those of a standard. For the U. S. P., standard preparations are supplied under the authority of the Board of Trustees of the U. S. Pharmacopeia; and for the B. P., by the National Institute for Medical Research, London.

PREPARATIONS IN THE U. S. P. REQUIRING BIOLOGICAL ASSAY

Digitalis and Strophanthin are tested by finding the minimal quantity required to arrest the cat's heart. The standard of comparison for digitalis is a powder of digitalis leaves, the potency of which has been carefully ascertained in relation to the International Standard Powder adopted by the Health Organization of the League of Nations. For Strophanthin the standard adopted is Ouabain.

Epinephrine preparations are assayed by comparing the rise in blood-pressure in anesthetized dogs caused by intravenous injections of the preparation and of a standard solution of epinephrine respectively.

Ergot.—Ergot, in the form of the fluid extract, is administered by intramuscular injection to single-comb leghorn cocks. Its potency per gram must be equivalent to not less than 0.5 mg. ergotoxine-ethane sulfonate when measured by the darkening produced in the comb of the cock. For the fluid extract of ergot the same standard of potency has been adopted.

Insulin is assayed by comparing its ability to lower the blood sugar of rabbits with that of the U. S. P. Zinc-Insulin Crystals Reference Standard. Other hormones are assayed by analogous procedures.

Pituitary Solution.—Pituitary solution is assayed by observing the contraction caused by it in the uterus of the virgin guinea-pig. The uterus is excised

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and suspended in oxygenated Ringer's solution and its movements are registered by attaching it to a lever writing on a rotating drum. The addition of pituitary preparations causes a marked contraction and this is compared with one caused by a definite amount of a standard powdered pituitary; 1 cc. of the solution of pituitary being equivalent in activity to 0.005 gram of the standard pituitary powder.

Cod-liver oil is tested for its vitamin A and D content through observations carried out upon rats kept under standard conditions and on a standard diet.

Preparations of other vitamins are assayed by similar methods or by means of microbiological procedures.

Liver and stomach preparations used for the treatment of pernicious anemia are tested for their potency by their ability to bring about certain changes in the blood of patients who are suffering from this disease and are in relapse, and subsequently to maintain a normal blood count in such persons. Authority over these products is vested in the U. S. P. "Anti-anemic Preparations Advisory Board."

Pepsin must digest 3000 times its weight of egg albumen when tested under the official conditions.

Arsphenamine and other arsenicals used in the treatment of syphilis have to comply with certain tests for toxicity as outlined by the National Institute of Health of the U. S. Public Health Service.

The various antitoxic sera are also standardized according to methods prescribed by the Public Health Service and their potency is designated in units.

PREPARATIONS IN THE B. P. REQUIRING BIOLOGICAL ASSAY

Digitalis.—The preparation is compared with a standard preparation by some method which measures the action on cardiac muscle. Two methods are recommended; the first determines the lethal dose in frogs by injection into the dorsal lymph sac; the end-point for the second is the amount required to produce arrest of the heart when injected intravenously at a slow rate in cats or guinea-pigs anesthetized and under artificial respiration.

Strophanthus.—Strophanthus is assayed in a similar way.

Neoarsphenamine.—Neoarsphenamine must comply with a test for absence of undue toxicity and with a test for therapeutic potency.

For toxicity, it is tested in comparison with the standard preparation on mice or rats, by the injection of doses given intravenously. For therapeutic potency, it is tested on a series of mice, or rats, infected with a suitable strain of pathogenic trypanosomes, such as Trypanosoma Equiperdum.

Sulfarsphenamine.—Sulfarsphenamine is tested in a similar way.

Pituitary (Posterior Lobe) Extract.—The activity of a sample of pituitary (posterior lobe) extract is determined by comparing its activity with that of the standard Preparation of Pituitary (Posterior Lobe) Extract by a biological method based on an action on the muscle of the uterus, or by the antidiuretic or pressor activity of such extracts.

Insulin.—The potency of a sample of insulin is determined by comparing the dose of it necessary to produce hypoglycemia in rabbits or convulsions in mice with the dose of the Standard Preparation of Insulin necessary to give the same effects. The retardation of the insulin effect of Protamine Zinc Insulin is determined by a similar procedure.

Vitamin A.—Young rats are fed on a diet deficient in vitamin A until they have ceased to grow. The effect on growth of the preparation to be tested is compared with that of a standard preparation. (A spectrophotometric method may also be used.)

Vitamin B_1.—The test is similar in character to that for vitamin A.

Vitamin C.—When guinea-pigs are given a diet free from vitamin C, symptoms of scurvy appear, *e. g.*, changes in the structure of the teeth or the occurrence of tender gums or hemorrhages. The degree of protection produced by the preparation to be tested is compared with that afforded by a standard preparation of *l*-ascorbic acid.

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Antirachitic (Vitamin Vitamin D).—(*a*) *Curative.*—Young rats are fed on a rachitogenic diet for about three weeks, and the degree of rickets produced may be determined by roentgen-ray photographs of the bones. The degree of healing produced in ten to fourteen days by the preparation to be tested is compared with that produced by a standard preparation.

(*b*) *Prophylactic.*—Two similar groups of young rats are fed on a rachitogenic diet, one group receiving daily doses of the preparation to be tested, the other of the standard preparation. The degree of prophylaxis is estimated by the average percentage of ash in the bones of the two groups at the end of about five weeks.

Antitoxins and Sera.—Biological standardization is required for antidysentery serum, antipneumococcus serum (Types I and II), diphtheria antitoxin, gas gangrene antitoxins (œdematiens, perfringens and vibrion septique), staphylococcus antitoxin, tetanus toxoid and tetanus antitoxin. The principle of the methods employed in each case is similar, the potency of the sample to be tested being compared with that of a standard preparation in their efficacy to protect animals against the toxic or lethal effects of a fixed dose of the particular toxin.

Old Tuberculin.—The potency of a sample of old tuberculin is tested by comparing the dose of it necessary to produce its specific toxicity in guinea-pigs or other animals infected with the Bacillus tuberculosis with the dose of the standard preparation of Old Tuberculin necessary to give the same effects.

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PART I

The Action of Inorganic Substances

I. WATER AND SALTS

WATER constitutes the principal component of the body, 70 per cent of which consists of this compound. It serves as the medium in which the colloids and crystalloids of protoplasm are dissolved. About 7 per cent of the total water of the body is present in the blood; 20 per cent is present in the interstitial fluids; while the remainder is present in the cells (intracellular fluid).

The living cell may be regarded as a solution of colloids and crystalloids surrounded by a limiting membrane. This membrane is composed of a complex colloidal mixture of lipoids and proteins and serves to preserve the integrity of the cell and to prevent the indiscriminate diffusion of substances from the protoplasm into the surrounding medium. Most animal cells are permeable to water and to some salts, and are therefore capable of changing their dimensions by absorbing or giving up water. The extracellular fluids of the blood, lymph and tissues are composed of a solution of salts and other substances in water; and unless the osmotic pressure of these fluids was maintained approximately equal to that of the cell contents, the cells, having walls permeable to water, would be subject to rapid changes in size and composition. In spite, however, of the great variations in the amount of water ingested and absorbed, in the amount of water eliminated by skin and kidneys, and the wide variations in the amount of salts in the diet, it is found that the body fluids maintain a remarkable constancy in the total percentage of salt that they contain and an even more remarkable constancy in the relative proportions of essential individual ions.

Soluble salts exist in the body mainly as ions, and each ion exerts the same osmotic pressure as an undissociated molecule. Seeing that different molecules and ions have quantitatively identical effects on osmotic pressure, it is possible to consider the osmotic changes produced by water and salts merely from the point of view of the total number of molecules and ions in solution, and regardless of any specific and chemical effects that these ions individually produce.

Molecules and ions in solution by their migration distribute themselves equally throughout a solvent. Thus when a solution of salt is brought into immediate contact with one containing sugar, the salt molecules and ions rapidly diffuse into the sugar solution and the sugar molecules into the salt solution until the whole becomes homogeneous, each fraction of the solution finally containing uniformly the same amount of sugar and salt. If a membrane were interposed between the two solutions of such a character that it was freely and equally per-

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meable to water, sugar and salt, the result would be the same. Cell membranes, however, are not equally permeable to water and solutes. Pure water diffuses readily into nearly all cells, but most dissolved substances meet with some resistance in entering cells, and different tissues vary in this respect. When a more dilute solution is separated from a more concentrated one by a membrane, which allows more ready passage of the solvent than the solute, uniformity of the system can only be obtained by passage of the solvent from the less to the more concentrated solution; and the latter will increase in volume. If this increase in volume be prevented by containing the solution within unyielding walls, a pressure will be developed which is called the osmotic pressure. The amount of this osmotic pressure depends upon the difference in concentration, but is independent of the type of ions and molecules on each side of the membrane.

For determining the reactions of animal cells to variations in the osmotic pressure of extracellular fluids, the red blood corpusles are particularly suited. They are easily obtainable, already separate, and the changes they undergo in size and shape can be readily observed. Within the envelope of the red cell are salts and colloids in solution, which solution therefore possesses a definite osmotic pressure. Water penetrates readily into these cells and when they are placed in distilled water, water passes into them until they swell up and rupture. Sodium chloride hardly penetrates the red blood corpuscles. The mere fact that, though they are continuously laved by the plasma, they contain a higher concentration of potassium and a lower concentration of sodium than the surrounding plasma, proves that the wall of the red cells must be very impermeable to these ions, which otherwise would soon attain the same concentration inside and outside the cell. When the red cells are placed in a solution of sodium chloride of the same osmotic pressure as (*i. e.*, isotonic with) that in the interior of the cell, there is no movement of water into the interior, since the water of the surrounding solution is held back by the sodium chloride. The corpuscles will, therefore, remain unaltered in shape and composition. If a solution of lower osmotic pressure (hypotonic) is employed, a certain amount of water is taken up from it by the cell, the weaker solution of sodium chloride being unable to compete with the attraction of the stronger solution in the interior of the cell. On the other hand, if a solution of higher osmotic pressure (hypertonic) be used, it withdraws water from the cell, because the salts in the interior are unable to retain the water against the stronger concentration outside.

Somewhat similar changes will occur in all animal cells as the result of changes in their osmotic environment. Thus a muscle immersed in distilled water will swell up from imbibition of water and soon lose its excitability. A heart is rapidly arrested if perfused with distilled water. Such tissues will, however, retain their configuration, and for a time their excitability, if kept in a solution of sodium chloride of the same osmotic pressure as the interior of the cells. For mammals such a solution contains 0.9 per cent of sodium chloride in distilled water. It is often called physiological or normal saline solution, but it must be

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remembered that it is "normal" only in respect of its osmotic pressure.

The cells in the body undergo continual readjustments in accordance with changes in the osmotic pressure of the body fluids, consequent upon variations in the absorption and elimination of water. The osmotic pressure of the blood, even under extreme physiological and pathological conditions, remains relatively constant. The maintenance of this constancy is one of the homeostatic mechanisms essential for the well-being of the organism, as the functioning and even the life of the tissues is only possible within a certain range of osmotic pressure above and below the normal. The changes that occur are also not of so simple a character as has been described for the behavior of red cells in a solution of sodium chloride, mainly because different cells show differences in selective permeability to different salts. Ammonium chloride, for example, in contradistinction to sodium chloride penetrates red cells readily, and in solutions of this salt the red cells behave almost as if they were placed in distilled water. They are readily permeable to urea but not to sugar. Cells may even differ in their permeability to water itself. For example, water is readily absorbed from the intestine but scarcely at all from the stomach, but this can scarcely be due to difference in the osmotic pressure of the interior of the cells lining these viscera. With these considerations it is possible to consider more generally the effects of water and salts.

1. **Water.**—Water penetrates into the superficial cells of the skin, which therefore become swollen and softened by prolonged immersion in it. Water is not absorbed into the circulation through the skin in mammals, but is absorbed more easily by less protected surfaces, and pure water applied to surfaces like the conjunctiva or nasal mucous membrane or the surface of a wound may cause irritation and pain from the disturbance of the normal relation of salt and fluid in the surface cells. Isotonic solutions, on the other hand, cause no pain.

The amount of water ingested in food and drink varies enormously. Very little absorption of water occurs in the stomach but it is rapidly absorbed in the small intestine, so that only about 250 cc. of fluid chyme passes through the ileocecal valve daily. Much of the remaining water is absorbed in the large intestine, especially in the cecum and ascending colon, the contents of which are still quite soft. Apart from ingested water there is an important internal circulation of water, as the amount in the salivary, gastric and intestinal secretions may be as much as 4 liters, which is almost completely reabsorbed before reaching the cecum.

When water is absorbed from the bowel and enters the blood stream, the dilution of the blood thus induced is so slight as to escape all but the most refined measurements. Nevertheless, this dilution suffices to stimulate the kidneys to excrete the excess fluid unless the organism is dehydrated, in which case the water passes into the tissues where it is retained. One of the functions of the kidney is to maintain constant the osmotic pressure of the plasma, which in turn is in equilibrium with the tissues.

When water is injected intravenously it does not lead to immediate

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diuresis as it is taken up rapidly by the tissue cells. The muscles and subcutaneous tissues especially take up considerable stores of water, which can be given up as required. When there is excessive loss of water, *e. g.*, from profuse sweating or diarrhea, the plasma becomes more concentrated and water can pass from the tissues into the plasma to restore the normal conditions. The concentration of salt in sweat is lower than that in the body fluids, so that sweating tends to concentrate the salts in the blood. This provokes thirst, and the ingestion of water again dilutes the plasma. All the factors concerned in water metabolism cannot be explained by simple diffusion and osmosis, and there is some evidence of a central, as well as a humoral, control of the water exchanges between the tissues and the blood. Pituitary extract has a remarkable effect in inhibiting water diuresis and the diuresis of diabetes insipidus, producing this effect by its action on the kidney.

A detailed consideration of all the factors involved in water exchange in the body belongs rather to the domain of physiology. Mention may be made here, however, of the deliberate use of water to effect a therapeutic purpose. Consideration of the value of spa waters may be deferred until the action of salt is considered as, though the effect of these waters is mainly due to the water, they usually contain more or less salt.

Water is used especially in febrile conditions to relieve thirst and to promote perspiration and diuresis. It tends to keep the mouth clean and wash out the stomach, as the latter absorbs little or none. It might be expected that a liberal supply of water would tend to keep the feces moist and so relieve constipation. It is ineffective for this purpose because most of the water ingested is absorbed in the small intestine, and in constipation the more prolonged residence of the contents in the large intestine gives longer time for absorption of the relatively small proportion of water that passes the ileo-cecal valve. If, however, a non-absorbable salt like magnesium sulfate be added to water, the absorption of water is checked and the feces become more fluid.

The administration of large quantities of water leads to a slight but measurable increase in the oxygen consumption (Fig. 2) which is attributable to the altered internal environment of the tissues as well as to the increased work of the heart and kidneys required for its elimination. There is also a slight increase in the nitrogen and sulfur eliminated in the urine. The amount of proteins and fats absorbed from the alimentary canal does not appear to be altered by the administration of large amounts of water.

Heavy Water or **deuterium oxide** differs from ordinary water in that hydrogen is replaced by an isotope of atomic weight 2 (deuterium) represented by the symbol D. Heavy water (D_2O) differs from ordinary water (H_2O) not only in its physical properties but in its pharmacological effects as well. D_2O melts at 3.8°, boils at 101.4°, has a specific gravity of 1.056 and is more viscous than H_2O. Administration of almost pure deuterium oxide, resulting in the body becoming 40 to 50 per cent saturated with it, causes death of mice in about seven days, the chief symptoms being loss of weight, fall of temperature, ataxia and dyspnea. Smaller amounts of D_2O (20 per cent saturation) cause an increase,

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larger amounts a decrease, of metabolic rate. Several effects suggest a sympathomimetic action, *e. g.*, a pilomotor response and the contraction of melanophores of Fundulus heteroclitus, which is prevented by ergotoxine and potentiated by epinephrine. Concentrations of over 90 per cent are fatal to tadpoles and to some worms and fish.

The substitution of hydrogen by deuterium has been studied also in other compounds. If the carbon-bound hydrogen of a physiologically

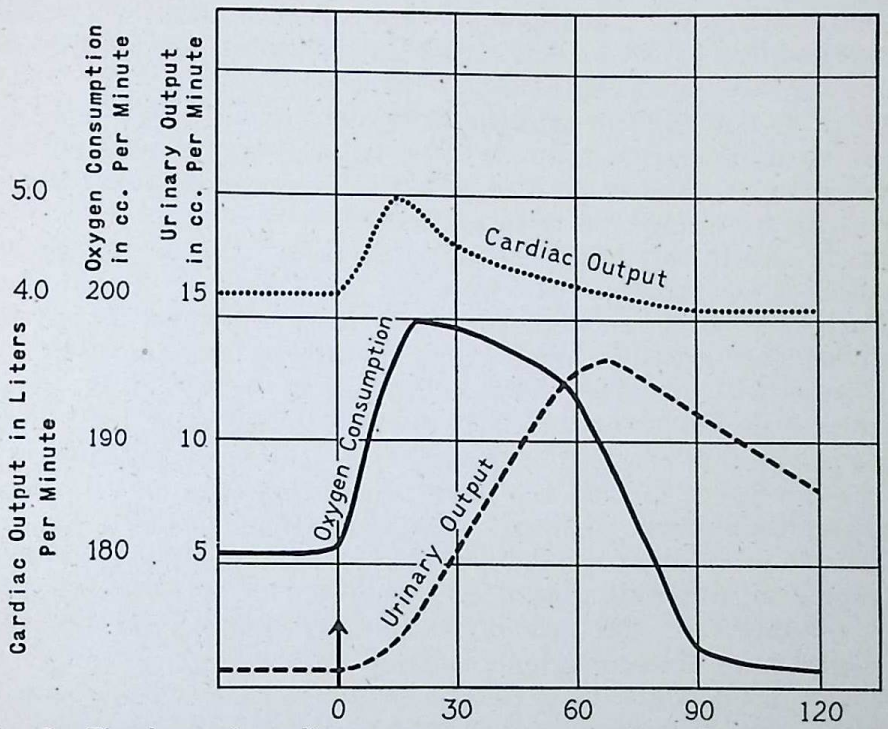

FIG. 2.—The changes in cardiac output, oxygen consumption and urinary output following the ingestion of a liter of water by a normal individual. The time in minutes following the ingestion of the water (indicated by the arrow at 0) is given as abscissæ.

active compound is replaced by deuterium, the metabolism of such compounds after administration to the animal can be studied by tracing the route taken by the deuterium. Similar studies have been made with compounds containing isotopes of other elements and the results of such studies with "tagged elements" has contributed greatly to our understanding of many metabolic processes.

PREPARATIONS

U. S. P. and B. P.

AQUA, water; AQUA DESTILLATA, distilled water; AQUA DESTILLATA STERILISATA, sterilized distilled water; AQUA PRO INJECTIONE, water for injection; U. S. P. AQUA STERILISATA, sterilized water, B. P.

INJECTIO DEXTROSI (U. S. P.), a sterile solution of dextrose in water for injection.

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2. **Sodium Chloride.**—The cation which contributes most to the osmotic pressure of the blood and interstitial fluids is sodium; within the cells, potassium fulfills the same rôle. With water, sodium chloride serves a most important function as the medium with which the cells are surrounded, and alterations in the salt concentration of the blood is reflected by a corresponding change in the interstitial fluid which in turn affects the water content of the tissue cells.

Weak (hypotonic) salt solutions generally produce effects similar to those, already described, due to water only. Isotonic salt solution is non-irritant and has no positive action. Strong salt solutions irritate, from withdrawal of water from the cells.

In the mouth salt has a characteristic taste. Salt in the diet has little effect on digestion apart from the fact that a small quantity of salt in the food renders it more palatable to most people and this increases the reflex flow of gastric juice. Large amounts of hypertonic salt solution causes withdrawal of fluid and shrinkage of the cells of the mucous membrane of the stomach, which may set up sufficient irritation to cause reflex vomiting. Part of this irritation may be due to penetration of the salt itself, because the more penetrating salts have a greater tendency to produce vomiting. Thus ammonium chloride produces vomiting more readily than sodium chloride; sodium sulfate less readily.

Little if any salt is absorbed from the stomach but it is freely absorbed from the intestine. The cells of the intestinal mucous membrane are so easily permeable to sodium chloride that hypotonic or isotonic solutions are absorbed almost as rapidly as pure water. The absorption of stronger solutions may be preceded by a period in which the fluid of the bowel actually increases, water diffusing into it from the blood. At the same time the salt is being absorbed and the solution eventually becomes isotonic and is absorbed.

The blood and interstitial fluids are affected by the osmotic changes consequent upon absorption of salt. The ingestion of isotonic saline and its entrance into the blood stream will cause a reduction in the colloid osmotic pressure of the blood. This in turn will result in a passage of fluid into the interstitial fluid but not into the cells as is the case following the ingestion of an equal amount of water. In other words, there will be a greater increase in blood volume and dilution of the blood and interstitial fluid following the ingestion of isotonic saline than occurs following the ingestion of water. This plethora induces a greater response on the part of the heart as shown in the increased cardiac output which follows the ingestion of normal saline. Since the kidneys also maintain a regulatory function on the blood volume, these respond to the ingestion of saline by an increased urinary output although this response is delayed as compared to that observed following the ingestion of water (Fig. 2).

When very large amounts of isotonic salt solution are thrown into

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the blood, the organism may have difficulty in excreting it rapidly enough, and the tissues are therefore found to be swollen and edematous in some parts of the body.

When salt solution is injected into the serous cavities or into the lymph spaces, absorption occurs in the same way as from the alimentary canal, except that in the case of the serous cavities diffusion seems to play a greater, and the other forces a smaller rôle, than in the stomach and intestine.

Strong salt solutions injected into animals either hypodermically or intravenously sometimes prove fatal, apparently from the withdrawal of fluid from the central nervous system. The symptoms in mammals are increasing lassitude and weakness, with augmented reflex excitability, tremors, and finally convulsions. The circulation is only slightly affected until just before death, when the blood-pressure falls suddenly. The red-blood cells are found to be much shrunken, and hemorrhages are found in different organs; the lungs are edematous, and the intestinal mucous membrane is swollen and congested.

The **Salts of the Urine** are increased by diuresis from any cause, as has been stated; both sodium and potassium are augmented, but especially the sodium, which is present in larger proportions in the plasma and therefore forms a larger constituent of the glomerular secretion. This increase in the sodium salts is, of course, particularly marked when diuresis is induced by common salt, but when potassium salts increase the urine, the sodium also generally predominates in it and this would eventually lead to the loss of all the sodium in the blood of herbivora, whose food contains large quantities of potassium; but after a certain amount of sodium has been lost, potassium causes no further excretion, so that the tissues are protected from the total loss of sodium chloride, which would be fatal to them.

In fevers, especially in pneumonia, the excretion of chlorides is often diminished. This is believed to be due to the tissues in fever taking up more water and chloride, reducing the volume and the chloride content of the blood.

Bunge states that in both man and animals a diet rich in potassium causes an appetite for common salt, while a diet which does not contain an excess of potassium does not develop this desire. Thus herbivorous animals and agricultural peoples seek for salt, because vegetable foods contain large quantities of potassium, while the carnivora and the hunting peoples require no salt and often have a distaste for it, owing to their food containing a larger relative proportion of sodium salts. This instinctive appetite he regards as a means by which nature protects the tissues from excessive loss of sodium.

Therapeutic Uses.—Water and salt are used for their local action, and for the supposed alterations in the tissue-change and in the excretions produced by them after their absorption into the blood. In general, patients are sent to watering places and baths, where, as Sir Walter Scott says, "the invalid often finds relief from his complaints, less from the healing virtues of the spa itself, than because his system of ordinary life undergoes an entire change, in his being removed from his ledger and account books—from his legal folios and progresses of title deeds—from his counters and shelves—from whatever else forms the main

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source of his constant anxiety at home, destroys his appetite, mars the custom of his exercise, deranges the digestive powers, and clogs up the springs of life." At the same time the drinking of large quantities of weak salt solutions, and the constant bathing in somewhat irritating fluids, may exercise a therapeutic action in many cases, and may at any rate aid the hygienic conditions. Whether the water contains salt or not, it must be remembered that in bathing the action is a purely local one, for neither the salt nor the water is absorbed. The slightly irritant effect on the skin may, however, improve its circulation and nutrition, and thereby be efficacious in some skin diseases.

The bath treatment has been recommended for numerous diseases in which the salt and water could not possibly have any beneficial action, and in which the remedial agent is the climate, and perhaps the faith of the patient in the water. Belief in the healing power of certain natural waters is one of the most ancient of all therapeutic theories, is found among altogether uncivilized peoples, and has been incorporated in many religions. It is not to be wondered at that in some nervous disorders the faith of the patient and auto-suggestion perform some marvelous "cures."

Salt in solid form or in strong solution is used occasionally as an emetic in cases of emergency, as in poisoning, and generally produces vomiting rapidly, owing to the irritant action on the stomach. In nitrate of silver poisoning it arrests the corrosive action by the formation of the insoluble silver chloride.

Salt solution is often used instead of water in enemata and when concentrated possesses an irritant action on the bowel, producing peristalsis. Strong solutions are sometimes thrown into the rectum to destroy thread worms.

The cramps and collapse which may follow exposure to heat is a result of the loss of sodium chloride in the sweat. Sodium chloride, usually in the form of 0.6 gram tablets, is therefore administered to those exposed to high temperatures in order to avoid the undesirable symptoms which follow profuse sweating. Sodium chloride is also administered in adrenal cortical insufficiency as described later (p. 556).

Isotonic salt solutions are often administered when the body has lost much fluid in order to replenish the depleted blood volume, as well as the fluid lost from the interstitial spaces. Such a condition is designated as dehydration and occurs in a number of clinical conditions. The simple administration of isotonic salt solution will remedy this deficiency but in many cases dehydration is complicated by other deficiencies which must also be remedied. For example, following hemorrhage, burns or other conditions accompanied by shock, the administration of saline is only of temporary benefit since the reduction in colloid osmotic pressure secondary to the loss of the blood proteins will allow the injected saline to rapidly diffuse into the interstitial fluid and thus be lost from the blood stream. Hence, in this case, the administration of blood or plasma is indicated. In other instances, dehydration is accompanied by the loss of excess base (as in diarrhea) or of chloride (as in vomiting) leading to acidosis or alkalosis and these must be remedied

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by the administration of the deficient anions and cations, respectively. Attempts have been made to utilize various colloids as substitutes for blood plasma. Acacia had a brief vogue and more recently gelatin, periston, a synthetic colloid, as well as other relatively non-toxic materials have been suggested. However, most of these substitutes exert deleterious actions as manifested by the increased sedimentation rate of the red blood corpuscles following their administration, and hence they have found no permanent place in therapy.

Sodium chloride in the form of intravenous isotonic saline is administered to overcome the dehydration following operations, vomiting, diarrhea, Addison's disease (*cf.* p. 556), diabetic acidosis, cholera and other conditions manifested by a state of shock, and decreased blood volume. Blood or plasma, if available, is indicated where there is a concomitant deficiency of blood cells or blood protein.

The isotonic salt solution ordinarily employed is inferior to the Ringer's solution, which contains the other salts of the alkalies in approximately the proportions in which they are found in the plasma (NaCl, 8.5 gram; KCl, 0.3 gram; $NaHCO_3$, 0.2 gram; and $CaCl_2$, 0.2 gram in a liter of distilled water). Excised organs live for many hours in this balanced solution, while they lose their vitality rapidly in an isotonic solution of sodium chloride. The presence of lime salts is particularly important.

The water which is used to dissolve the salts must be recently distilled and kept aseptic; otherwise the fluid, if injected intravenously or hypodermically, is liable to cause fever symptoms from the presence of toxic substances derived from dead bacteria. If injected too rapidly or in individuals in whom the renal or cardiac functions are deficient, the administration of excessive amounts of saline may lead to pulmonary edema which may prove fatal if severe, or to edema of the tissues. The promiscuous use of saline injections is thus to be deprecated. Where edema exists as a result of heart or kidney failure, the administration of a diet low in sodium content aids in the removal of this dropsy.

Preparations

Liquor Sodii Chloridi Isotonicus, (U. S. P.) physiological solution of sodium chloride. 0.9 per cent sodium chloride in distilled water.

Liquor Sodii Chloridi Physiologicus (B. P.), physiological solution of sodium chloride, physiological saline solution, normal saline solution.

Injectio Dextrosi et Sodii Chloridi (U. S. P.), a sterile solution of dextrose and sodium chloride in water.

Injectio Sodii Chloridi et Acaciæ (B. P.), a sterile freshly prepared solution of sodium chloride and acacia.

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3. **Saline Diuretics.**—The amount of urine is increased by all solids which are eliminated by the kidney, as well as by an excess of fluid in the blood. For the kidney is unable to excrete solids except in solution, and every molecule which is passed through it carries with it a certain amount of water to augment the secretion. Only substances which can circulate in the body in considerable quantities can be used to increase the urine in this way, and in practice the chief diuretics of this class are comprised of the indifferent salts and similar harmless bodies. In order to act as diuretics these must be readily absorbed from the alimentary tract and this excludes a large class of salts which increase the urine greatly when they are injected intravenously, but which are absorbed with difficulty and are therefore used mainly for their effects on the intestine (see Saline Cathartics, p. 239).

Among the saline diuretics are the chlorides of sodium, potassium and ammonium, though these are seldom prescribed for this purpose; their diuretic action is seen, however, in the treatment at spas and water-places. The cerebral action of the bromides precludes their use as diuretics, though an increased secretion of urine accompanies their use in therapeutics. The iodide of potassium is often added to other diuretics to reinforce their action, but is liable to induce other symptoms when given in large quantities. The typical saline diuretics are the nitrates of the alkalies and the urea group.

The **Nitrates** have a cool, saline taste, and ordinary doses taken in water have no effect except to produce an augmented flow of urine. They have long been used as diuretics, more especially the nitrate of potassium. The diuresis is generally attributed to the salt-action, which increases the exchange of fluid between the blood and lymph and thus promotes the filtration in the kidney. The presence of nitrate and potassium ions in the filtrate retards the reabsorption of fluid in the tubules and thus leads to a larger proportion reaching the ureters.

Large quantities in concentrated solution may cause gastro-intestinal irritation, giving rise to pain in the stomach region, nausea, vomiting, and sometimes diarrhea, and blood may be present in the vomited matter and in the stools. The urine is often abundant, but may be scanty or entirely suppressed. In rare cases these symptoms are followed by muscular weakness, apathy, collapse, and eventually coma and death. At the autopsy the stomach and intestines are found red and congested, and contain blood extravasations. The kidney is said to have presented the symptoms of acute nephritis and hemorrhages in some cases of poisoning.

The effects of nitrates are for the most part those of an indifferent and diffusible salt, but it is possible that this may be reinforced by some further irritant action, for smaller quantities of the nitrates than of the chlorides are sufficient to induce irritation, and solutions of the nitrates isotonic with the blood cause irritation and congestion in the intestine and are slowly absorbed. This irritant effect of the nitrates has been explained as the result of the reduction of the nitrates to nitrites in the alimentary canal and tissues, but no symptoms of nitrite action seem to have been observed in cases of poisoning with nitrates.

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Haldane has shown that nitrite is formed from the nitrate used in the preservation of meat by salting, and that some nitrous-oxide hemoglobin is formed and gives a bright red color to the meat.

Water itself, as we have seen, is an excellent diuretic. The nitrates of the alkalies have also been used for this purpose, particularly potassium nitrate. A more powerful diuretic which is less apt to cause the gastrointestinal irritation or the toxicity sometimes seen following the use of the nitrates, is urea. Twenty grams of urea given by mouth produce a rapid diuresis and normally the whole of the urea is excreted within twenty-four hours. Urea obviously should not be used in conditions in which its excretion is deficient as evidenced by an elevation in the urea content of the blood.

Ammonium Acetate and **Citrate** are indifferent salts but undergo oxidation in the tissues and finally form urea which acts as a diuretic in passing through the kidney. They were formerly supposed to increase the secretion of sweat but this action is insignificant.

Therapeutic Uses.—The saline diuretics are seldom used except as ingredients of diuretic mixtures; *e. g.*, along with digitalis, or to render the urine more dilute and thus to reduce its acidity in irritation of the genito-urinary tract. Where it is merely desired to increase the volume of the urine, the ingestion of water, fruit juices, or other liquids suffices to induce the desired diuresis. Where more effective diuresis is desired, as in edema, the purine derivatives and organic mercurials are generally used (p. 142 and p. 393).

PREPARATIONS

U. S. P. and B. P.

POTASSII NITRAS, nitre, saltpeter (KNO_3); colorless crystals with a cool, saline taste, very soluble in water, prescribed in dilute solution. Dose 1 gram (U. S. P.); 0.3 to 1 gram (B. P.).

UREA, $CO(NH_2)_2$, colorless crystals with a cool saline taste, soluble in equal parts of water. Dose, 8 grams (U. S. P.); 1 to 16 grams (B. P.).

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II. SALTS OF THE ALKALIES

1. **Potassium Salts.**—Potassium is the important cationic constituent of the intracellular fluid being present in an amount which osmotically balances the sodium of the extracellular fluid. It is present in the blood in a concentration of about 20 mg. per 100 cc. Potassium constitutes an important and vital component of the cell and body fluids. Animals fed a diet practically devoid of the element soon die but since this element is present in large amounts in many foodstuffs, a deficiency of it is not encountered clinically.

Although an essential constituent of the body cells and fluids, potassium is toxic when present in excessive amounts. Following an intra-

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venous injection of potassium chloride, this toxicity is manifested chiefly on the central nervous system and heart. In mammals the chief nervous symptoms are great muscular weakness and apathy. The respiration becomes rapid and labored, probably from the anemia of the center. Potassium first increases the activity of the spinal centers and then paralyzes them in mammals, but this is concealed by the depression of the heart when the drug is injected intravenously.

The depression of the heart is shown in the frog by weakness, slowness and irregularity when chloride of potassium solution is injected subcutaneously, but is more clearly demonstrated by the rapid failure of an excised heart when a chloride of potassium solution is perfused through it. An isotonic solution of common salt may restore the heart beat after it has been stopped by potassium, which proves conclusively that the latter has a specific poisonous action in addition to any salt-action. Ringer found that the beat of the frog's heart perfused with a solution of common salt was not so satisfactory as that of one perfused with the same solution to which some potassium salt had been added, probably because when the fluid perfused contains no potassium, some of the salts of that metal diffuse out of the muscle cells and this disturbs the ratio between the potassium and sodium which is necessary to life.

The mammalian heart is also injured by the action of potassium when the salt is injected intravenously, as is shown by weakness and dilatation, slowness of the pulse, heart block, and finally by ventricular fibrillation not infrequently; the fibrillation is due to a combination of increased automaticity and intraventricular block (Nahum and Hoff). The blood-pressure falls abruptly partly from this action on the heart, which appears to be a direct one on the muscle, but a reflex vasodilation from an action on the carotid sinus may also play a part (Hauss and Shen). The poisonous action of potassium on the heart has given rise to exaggerated apprehensions of the danger of using its salts in therapeutics, and it may therefore be noted that potassium has no effect on the heart when given by the stomach, and that very much larger quantities of potassium are taken daily in the food by thousands of persons than are ever prescribed in medicine. The absence of effects from the potassium ion when the salts are taken by the mouth is due to their rapid excretion in the urine.

The failure of the heart is the cause of death in mammals when potassium salts are injected into a vein, the respiration and the reflexes often persisting for a few seconds afterward. In the dog the heart is arrested in systole when the blood concentration is three or four times the normal. When potassium salts are injected into an artery, so that they can reach the peripheral vessels before the heart, they cause marked vasoconstriction with an abrupt rise in the blood-pressure; this action appears to be a direct one on the walls of the arterioles for the most part, though it is possible that this is reinforced by stimulation of the medullary and spinal vasomotor centers.

Potassium also plays a rôle in the transmission of the nerve impulse, the release of acetylcholine being associated with a diffusion of potassium from the nerve cell. Conversely, potassium simulates to some extent

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the action of acetylcholine so that for a time it was believed to represent the chemical mediator of cholinergic nerve fibers. Excessive amounts of potassium reduce the excitability of the nerves and the amplitude of their action current. Potassium also exerts an anti-curare action.

Therapeutic Use of Potassium.—Apart from the superior diuretic action of the potassium over the sodium ion, there is little to choose for most purposes between potassium and sodium salts. In some cases the potassium salt may be more suitable because of some physical property, *e. g.*, potassium bromide is less deliquescent than sodium bromide, in other cases the preference for potassium salts is merely traditional. The salt most commonly employed as a diuretic is potassium acetate, the nitrate being now rarely used. Recently caution has been urged against the indiscriminate use of potassium salts in Bright's disease as the retention of potassium may cause cardiac failure. Likewise in Addison's disease where there is an accumulation of potassium in the blood, the use of a diet low in potassium is desirable. Conversely, an adequate intake of potassium is necessary when desoxycorticosterone is administered since this drug tends to reduce the potassium content of the blood.

Recent clinical experience has shown that potassium has a definite effect on the contraction of voluntary muscles, either on the peripheral neuromuscular transmission or on the contractile response of the muscles. In the condition known as "familial periodic paralysis" the serum potassium is abnormally low during the paralytic attacks, paralysis developing when the serum potassium falls below 12 mg. per 100 cc. Administration of potassium chloride by mouth in doses of 5 to 10 grams raises the serum potassium and abolishes the paralysis. Large doses of potassium chloride also cause some improvement in muscular contraction in myasthenia gravis. Potassium chloride in doses of 2 to 5 grams, three or four times daily has also been used in the treatment of Ménière's disease but its mechanism of action in this disorder is not clear.

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2. **Lithium, Cæsium, Rubidium.**—In regard to the action of the rare alkalies, Lithium, Cæsium and Rubidium, comparatively little is known. They seem to have some effect in depressing the spinal cord in the frog, but it is uncertain whether this is, like the action of sodium chloride, merely due to the presence of large quantities of salts in the body, or whether they have a specific action on the nerve cells. Lithium seems to have some further depressant action on the motor nerves, and to weaken the muscular contraction. It acts much less powerfully on the mammalian heart than potassium, but has some effect in weakening it. Its chief effects are exercised in the alimentary tract, for gastro-

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enteritis and extravasations of blood into the stomach and bowel are induced by its subcutaneous or intravenous injection and these are the cause of death in fatal poisoning in animals. Such violent effects are less easily elicited by the administration of lithium by the mouth, though vomiting and purging have been caused in animals by this method also, and disturbance of the alimentary tract has sometimes followed from lithium treatment in man. Some of the lithium is excreted in the bowel, and in this respect this metal appears to form a contrast to potassium and sodium and to resemble rather the group of alkaline earths. Most of it appears in the urine, however, and here the excretion is slow, for traces may be found in it for many days or even weeks after a single administration.

Rubidium seems to act on the frog's heart and on muscle cells in much the same way as potassium. It is slowly excreted by the kidneys; traces are found also in the feces, especially if diarrhea occurs, as is not infrequently the case.

Cæsium resembles lithium in causing inflammatory reactions in the alimentary tract, leading to vomiting and diarrhea, when it is injected hypodermically or when large doses are given by the mouth. It is partly excreted along the alimentary tract in mammals. In the frog it induces weakness of the muscles and paralysis. According to Kisch, cæsium salts have an action on the excitability of the frog's heart similar to that of calcium but on its contractility similar to that of potassium.

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3. **Ammonium.**—Although ammonium is not a metal, its behavior in the body resembles in many points that of the fixed alkalies, and it may therefore best be studied along with them. The solutions of ammonia and the gas itself are strongly alkaline and therefore powerful irritants, and the general action of the ammonium ion can be determined only by the examination of those of its salts in which, as in ammonium chloride, the effects of the anion can be neglected. The action of chloride of ammonium is due to the specific action of the base and to the salt-action.

Action.—Its most striking effect is the stimulation of the **Central Nervous System**, which is induced when it is injected subcutaneously or intravenously. The reflex irritability is much increased, and this may be followed by tetanic convulsions, both in frogs and mammals. These convulsions persist after division of the cervical spinal cord and destruction of the medulla oblongata and brain, and are evidently caused by changes in the spinal cord, similar to those met with in strychnine poisoning. The medullary centers are also involved, for the respiration very often ceases for a moment, and then becomes much accelerated, and in some instances deeper, from stimulation of the center.

The blood-pressure rises from contraction of the peripheral arterioles, induced by stimulation of the vasomotor center, while the heart is sometimes slowed from increased activity of the inhibitory center, but is said to be accelerated in other cases; whether this arises from action on the cardiac muscle or on the accelerator center is still unknown.

During the convulsions the respiration is arrested and the blood-pressure becomes extremely high. If large enough quantities be injected,

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the stimulation is followed by paralysis of the central nervous system and the animal dies of asphyxia, but if artificial respiration be carried on, it recovers rapidly, from the salt being eliminated.

In the frog ammonium chloride tends to paralyze the terminations of the **Motor Nerves**, but little or no such action is met with in mammals. This marked curare-like action differentiates the ammonium tetanus of the frog from that seen under strychnine, as the spasms last a shorter time, and soon become weaker, from the impulses failing to reach the muscles through the depressed terminations. The **Muscles** themselves are also acted on by ammonium in much the same way as by potassium. Ammonium chloride is credited with rendering the mucus secretion of the stomach and bronchi more abundant and less tenacious, but there seems little foundation for this belief.

Ammonium salts penetrate most cells of the body more freely than the salts of the fixed alkalies, and solutions of ammonium chloride are therefore **absorbed** more rapidly from the stomach and intestine than those of sodium or potassium chloride. They permeate into the blood cells with still greater freedom, and, in fact, solutions of the chloride of ammonium meet with little more resistance in entering the red-blood corpuscles than does distilled water. If ammonium be combined with a non-permeating ion it penetrates the blood cells or the intestinal epithelium with difficulty, however, so that the sulfate of ammonium is slightly cathartic, although less so than the sulfates of the fixed alkalies. (See Saline Cathartics.) The epithelium of the lungs has been stated to be impermeable by the ammonium ion, but this appears to be incorrect (McGuigan).

When ammonium salts are taken by the mouth, they have little or no tendency to cause symptoms from either the central nervous system or the heart. No case is known in which convulsive attacks could be shown to be due to the direct action on the central nervous system in man, and it is very doubtful whether the circulation is affected at all. In some cases of poisoning with ammonium hydroxide, convulsions have occurred, but these seem to be due to the violent irritation caused by the strong alkali.

Excretion.—Some ammonium is excreted unchanged in the urine, while some is changed to urea. This transformation, which probably takes place in the liver chiefly, proceeds very rapidly, so that considerable quantities may be injected slowly into a vein without inducing any symptoms whatever. This formation of urea occurs more readily in the herbivora than in man and the carnivora, and is especially seen when the ammonium is given in the form of the carbonate or of salts which are oxidized to the carbonate in the body, such as the acetate and citrate; in the herbivora the abundant fixed alkali of the blood and tissues displaces the ammonium of such salts as the chloride, and the carbonate of ammonium thus formed is changed to urea, while in the carnivora and man, the supply of fixed alkali is less abundant and the ammonium chloride is not changed to the same extent.

When ammonium chloride is ingested, the NH_3 portion reacts with carbon dioxide to form urea, liberating hydrochloric acid. This causes

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a reduction of the alkaline reserve of the blood. Large doses of ammonium chloride produce acidosis with resulting hyperpnea and a fall of CO_2 tension. This is accompanied by diuresis, apparently because the acidosis causes a loss of salt and water from the cells into the extracellular fluid, and diuresis is produced by the salts and water thus liberated in the blood.

Ammonium salts of the inorganic acids and of benzoic acid all produce an acidosis as described while this is apparently not true of ammonium acetate, perhaps due to its rapid destruction and removal as carbon dioxide by the lungs.

The urine is often increased by the exhibition of ammonium salts; ammonium nitrate apparently being the most active. It is to be noted that, while the alkaline salts of the fixed alkalies render the urine less acid or even alkaline, ammonium salts have no such effect, because they are excreted as urea or as neutral salts.

In birds and reptiles ammonia is excreted as uric acid.

The **Substituted Ammonias** of the methane series, such as methylamine, and some of those of the aromatic series resemble ammonium in their general effects, but the stimulation of the central nervous system is not often so marked. In general terms, those compounds in which one hydrogen atom is substituted, tend to cause greater nervous stimulation than those in which two or three such substitutions are made, while this action is again more prominent in those in which four alkyl groups are combined with the nitrogen. In addition, most of these compounds seem to have a more depressant action on the central nervous system afterward than ammonium, and they all tend to weaken and eventually to paralyse the terminations of the motor nerves. Some of them slow the heart by an action resembling that of muscarine, while others act on the peripheral ganglia like nicotine.

The ammonium bases formed from the natural alkaloids appear to have less action on the central nervous system, but act like curare on the terminations of the motor nerves.

Trimethylamine oxide is of interest in the fact that it occurs as a normal constituent of the blood in certain fishes in which it plays an important rôle in nitrogen metabolism.

Therapeutic Uses.—Ammonium chloride is prescribed chiefly for its effects on the respiratory mucous membranes, and is a very common constituent of expectorant mixtures for bronchitis and catarrh. It acts as an expectorant mainly by reflex irritation of the stomach, and increases the bronchial secretion. A lozenge is often used for sore throat, and chloride of ammonium solutions are occasionally inhaled or sprayed into the throat. It has also been prescribed in gastric catarrh with benefit in some cases, but whether this is due to its acting on the mucous secretion is unknown.

Ammonium chloride solution may be injected intravenously in cases of alkalosis. When used for this purpose, it must be injected very slowly in the form of a sterile 0.8 per cent solution in water.

Ammonium chloride is prescribed in the form of enteric coated tablets to increase the acidity of the urine and as a diuretic. It is given in doses of 1 to 2 grams, four times a day, and may be used in conjunction with digitalis or the mercury diuretics.

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Aromatic spirits of ammonia is used as a stimulant by inhalation or orally in a dose of 2 cc. well diluted with water.

PREPARATIONS

AMMONII CHLORIDUM, ammonium chloride (NH_4Cl), a white, crystalline powder, odorless, with cool saline taste. Soluble 1 in 3 of water. Dose, U. S. P. as expectorant, 0.3 gram, as diuretic 3 to 6 grams daily; B. P., 0.3 to 4 grams.

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III. SALTS OF THE ALKALINE EARTHS

1. **Calcium.**—Calcium is the most abundant mineral present in the body, approximately 2 per cent of the body weight being comprised of this element. It plays a rôle as a constituent of the skeleton, in the coagulation of the blood and in the maintenance of normal neuromuscular irritability.

Calcium and the other alkaline earths differ from the alkalies in possessing comparatively few very soluble salts, and they seldom effect such changes in the physical properties of the fluids of the body as have been described under salt-action and chloride of sodium. Even the soluble salts penetrate with greater difficulty into the various tissues of the body, which seem to have less affinity for them than for the salts of the alkalies. They precipitate colloids, such as the proteins, in more dilute solutions than the salts of the alkalies, and the precipitate is not redissolved by dilution with water. This precipitation of proteins appears to account for the pain and irritation which follow the subcutaneous injection of the more readily dissociable salts such as the chloride.

Action.—The soluble lime salts are **Absorbed** with difficulty from the stomach and intestine and retard the absorption of fluid. They would presumably have a cathartic action were they not thrown out of solution very readily by the alkaline fluids. In addition, calcium forms insoluble salts with all of the cathartic anions. The greater proportion of the lime, taken either in the food or as a remedy, unquestionably leaves the body in the stools unabsorbed, while a smaller quantity of it is taken up from the alimentary canal whether the lime be administered in a soluble or in an insoluble form. This circulates in the blood, partly as diffusible salts but partly in combination with proteins, and is slowly excreted, unless there is a deficiency in the supply of lime, when it may be utilized by the tissues. When larger quantities are thrown into the blood by intravenous injection, the calcium of the blood remains abnormally high for a short time, but all the calcium thus injected is not in the circulation throughout its stay in the body. Some of it is temporarily deposited and is gradually withdrawn and excreted after the first excess is eliminated.

The absorption of calcium takes place from the upper part of the small intestine. The amount absorbed from the diet varies depending

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upon the motility of the bowel, the presence of fatty acids which form insoluble soaps, the acidity of the intestinal contents and the presence of phosphates and other cations which form insoluble calcium salts. Acidity favors the absorption of calcium. Vitamin D is also an essential factor for the normal absorption as well as the utilization of calcium.

The *serum* in health contains 9 to 11.5 mg. Ca per 100 cc. Of this only about 4.25 to 5.25 mg. exist as calcium ions. The remainder is in some indiffusible combination with protein. The Ca in the serum is remarkably constant, so that some mechanism must exist to maintain a balance between absorption, deposition and elimination. Factors which have been found to assist in controlling the concentration in the serum are the amount and availability of the calcium in the food, the body stores, the reaction of the tissue, the presence or absence of vitamin D, and the parathyroid hormone.

The normal calcium requirements for a healthy adult have been estimated at 0.8 gram of calcium per day. This is a minimum amount and more is required during growth, pregnancy or lactation. An ill-balanced diet may easily contain too little calcium. Cow's milk contains about 0.12 per cent of calcium, about five times as much as human milk. A pint of cow's milk provides a full day's ration of calcium in an easily assimilable form.

Approximately one-fourth of the ingested calcium is excreted in the urine, the remainder appearing in the feces. Even during starvation small amounts of calcium continue to be excreted by the bowel.

The total calcium content of the serum varies considerably in response to changes in the inorganic phosphate and protein content of the blood. The ionic calcium content, on the other hand, remains relatively constant under these conditions. Since it is this ionic calcium which is physiologically important, symptoms will not occur unless the concentration of this fraction is altered. A diminution, as seen in hypoparathyroidism, results in tetany which is marked by hyperirritability of the neuromuscular system. An increased concentration of ionic calcium such as is observed in hyperparathyroidism results in a diminished irritability of the neuromuscular system.

Calcium deficiency is observed chiefly in avitaminosis D in which the absorption and utilization of calcium is defective leading to rickets in childhood and osteomalacia in the adult. Abnormalities in function of the parathyroid glands also induce changes in the calcium metabolism (*cf.* p. 550). Long continued diarrhea (by interfering with the absorption of calcium), renal insufficiency, as well as diets deficient in calcium may all lead to a loss of calcium salts from the bones (osteoporosis).

Balanced Salt Solutions.—A curious relationship has been shown to exist between the calcium and potassium salts. Thus when a frog's heart is perfused with sodium chloride solution containing a trace of calcium, the movements are not entirely normal, the contraction being somewhat prolonged and the relaxation much retarded. If a trace of potassium chloride is added, however, the contraction becomes normal in character. On the other hand the effect of potassium on the frog's heart is antagonized by the addition of lime. The same holds true for voluntary muscle, the salts of calcium tending to neutralize the effects of potassium, and *vice versa*, and in several other relations an antagon-

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ism has been observed between these two metals. Another marked antagonism was shown by Meltzer, that toxic quantities of magnesium can be completely neutralized by calcium. And, as the symptoms of magnesium poisoning in mammals are characteristic, the recovery of animals when calcium is injected is very striking; magnesium induces narcosis and anesthesia, which is immediately counteracted by calcium, and the animal assumes its normal posture.

Another question of interest is the relation between sodium and calcium. It has already been noted that the frog's heart perfused with sodium chloride solution soon ceases to beat, but can be restored by the addition of calcium and potassium to the circulating medium. The ordinary explanation (Ringer, Howell) is that the calcium and potassium are necessary to the activity of the heart and that when pure salt solution is perfused these elements diffuse into it and are lost from the heart muscle; this diffusion is prevented if calcium and potassium be contained in the solution, and the heart, retaining the salts essential to its activity, continues to beat. Another explanation has been offered by Loeb, who supposes that the lime and potassium are not directly essential, but that they neutralize the poisonous effects of sodium. This poisonous action of sodium has not been generally recognized, but is well shown by the behavior of a small fish (fundulus) living in salt water, which can be transferred to distilled water without injury, thus showing that neither sodium nor calcium is necessary in its environment. But if it be put in sodium chloride solution of the same strength as sea water, it dies, so that sodium is poisonous to it unless when antagonized by the other constituents of sea water; the essential elements are calcium and potassium, for when these are added to the injurious sodium solution, the fish lives as well as in sea water. This series of experiments certainly forms a strong support for Loeb's theory that calcium is not directly essential to rhythmic movement, but only neutralizes the effects of sodium. On the other hand, the calcium salts themselves are poisonous when they are not counterbalanced by sodium and potassium; in this, as in many other instances, there must be maintained between the inorganic constituents of the surrounding fluid an equilibrium, such as exists in sea water in the case of the fundulus, and in the blood plasma in the case of the heart and other organs.

Lime salts are also indispensable in some processes which are not dependent on the presence of living cells. Thus rennet does not coagulate milk except when a lime salt is present, and the **Coagulation of the Blood** may be prevented by precipitating its calcium salts in the form of oxalates. The fibrin-ferment is not formed except in the presence of calcium salts, and when oxalates are added to the blood before this ferment is developed, they prevent its formation and hinder clotting. When lime salts are added, the ferment is liberated and coagulation occurs at once. In other words, lime is not necessary for the activity of the fibrin-ferment, but for its development from the prothrombin in which it exists in the circulating blood.

Therapeutic Uses.—Calcium is used therapeutically in conditions of abnormalities of calcium metabolism in which there is a deficiency of this element.

During *pregnancy* the constant demand on the part of the growing fetus for calcium puts a heavy tax on the calcium metabolism of the maternal tissues and the serum calcium is frequently somewhat diminished especially toward the end of pregnancy. A low serum calcium has also been found in eclampsia. It is important that the maternal diet should contain a liberal daily ration of calcium both during pregnancy and during lactation, when the calcium requirements may be nearly doubled. The condition of osteomalacia occurring in pregnancy is not,

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however, arrested merely by giving calcium salts in food, but is prevented if vitamin D be given in addition.

In *tetany*, the administration of calcium salts induces a rapid subsidence of the carpopedal spasm, twitchings and other symptoms characteristic of this disorder. For prompt relief when necessary the intravenous injection of 5 to 20 cc. of a 5 per cent solution of calcium chloride or a 10 per cent solution of calcium gluconate is indicated. The latter salt is less effective than the former but is also less irritating. In the case of calcium chloride, great care must be taken that the injection be made slowly and that none of the solution escapes from the vein. Otherwise a slough will result. Intravenous calcium is only used for the relief of the acute symptoms. The condition is then managed by the use of specific substitution therapy (*cf.* p. 551) and calcium by mouth. For the latter purpose a 25 per cent solution of calcium chloride in the syrup of glycyrrhiza may be given in doses of 10 cc. several times daily. Calcium lactate or calcium gluconate are less apt to induce gastric irritation and may be given in large doses (10 to 25 grams daily). They are best given mixed with milk, fruit juices or sprinkled over cereals in divided doses throughout the day.

Calcium salts are also administered in conjunction with vitamin D in conditions in which there is a deficiency of lime in the bones as in osteomalacia, osteonephropathy or other conditions associated with generalized osteoporosis. Citric acid or fruit juices may be added to aid in the absorption of the calcium from the gut.

Because of its effects in modifying permeability and blood coagulation the use of calcium salts has been recommended in such diverse conditions as urticaria, angioneurotic edema, purpura, etc., but there is no evidence to indicate their value in these disorders. Calcium chloride or gluconate are injected occasionally to relieve the spasm of intestinal, ureteral or gall bladder colic or abdominal spasm which follows the bite of poisonous spiders or other insects.

The preparations of the **oxide** and **hydrate** owe their activity chiefly to their alkalinity and not to the calcium, but differ from the hydrates of the alkalies in their insolubility and in their slow absorption. Lime water tends to neutralize the gastric juice and has an astringent effect in the intestine which is probably due to its forming an insoluble compound with the surface proteins, in the same way as tannic acid. Lime water is used in some dyspeptic conditions, especially in vomiting. It is often added to milk in intestinal irritation in children and in typhoid fever, as it is said that milk thus treated coagulates in finer particles than when given alone, and is better digested and less liable to disturb the intestine. Lime water or syrup of lime is also used as an intestinal astringent in diarrhea, especially in children. As an antacid in the stomach, lime is inferior to magnesia and other alkalies, because it tends to delay the evacuation of the contents. Lime water is not applicable in cases of acid poisoning, as it contains much too little of the base to be serviceable, but the syrup may be used, or lime shaken up with water (milk of lime). The treatment with lime is specially indicated in cases of oxalate poisoning.

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Lime water has been used externally as a protective, mildly astringent application to ulcers, and the lime liniment, no longer official, was formerly much used in the treatment of burns. It derived its name of Carron oil from having been used for this purpose in the iron works at Carron.

The preparations of the **carbonate** of lime are used as antacids in hyperacidity of the stomach, especially when this is combined with a tendency to diarrhea. The mixture, or the aromatic powder B. P., is the form generally used, and may be prescribed with opium or with other astringents.

Externally, prepared chalk is used as a powder to protect irritated parts of the skin and occasionally in ulceration; it is the chief ingredient in many tooth powders.

PREPARATIONS

CALCII CARBONAS PRÆCIPITATUS, precipitated chalk (U. S. P.); CALCII CARBONAS, calcium carbonate (B. P.), ($CaCO_3$), a fine, white, microcrystalline powder, practically insoluble in water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

CALCII CHLORIDUM (U. S. P., B. P.) ($CaCl_2$), a white salt with a sharp, saline taste, very deliquescent and soluble in water. Dose, U. S. P., 1 gram; B. P., 0.6 to 2 grams. By intramuscular injection, 0.03 to 0.1 gram; by intravenous injection, 0.3 to 1 gram.

CALCII CHLORIDUM HYDRATUM (B. P.), hydrated calcium chloride, ($CaCl_2$, $6H_2O$). Dose, intramuscularly, 0.06 to 0.2 gram; intravenously, 0.6 to 2 grams.

Calcium chloride is the salt which gives the least complicated calcium action. It has a strong attraction for water and is readily dissociable and is therefore more irritant than the chlorides of the alkalies and other alkaline earths; it ought to be prescribed only in dilute solution, and should not be injected into the subcutaneous tissues or muscle, as it causes great pain and sometimes even sloughing. Instead of the chloride, the lactate has been employed in the same doses and has the advantage of dissociating more slowly and thus causing less pain and irritation when it is injected.

CALCII GLUCONAS, ($Ca(C_6H_{11}O_7)_2H_2O$). Dose, U. S. P., oral 5 grams, intravenous 1 gram; B. P., 2 to 4 grams. Calcium gluconate has been extensively used in recent years as a substitute for the chloride or lactate. It is a white granular powder, slowly soluble in water.

INJECTIO CALCII GLUCONATIS (B. P.), injection of calcium gluconate. Dose, 10 to 20 mils.

CALCII HYDROXIDUM (B. P.), slaked lime ($Ca(OH_2)$, a soft white powder, slightly soluble in water. Dose, 0.3 to 1 gram.

LIQUOR CALCII HYDROXIDI (U. S. P., B. P.), lime water, is a saturated solution of calcium hydrate or slaked lime and contains about 0.15 per cent. It is a clear fluid with a saline and feebly caustic taste. Dose, U. S. P., 15 cc.; B. P., 30 to 120 mils.

CALCII LACTAS (U. S. P., B. P.) ($Ca(C_3H_5O_3)_2,5H_2O$), a white almost tasteless powder soluble in 18.5 parts of water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

TABELLÆ CALCII LACTATIS (B. P.), tablets of calcium lactate. Dose, 1 to 4 grams.

CALCII PHOSPHAS TRIBASICUS (U. S. P.), CALCII PHOSPHAS (B. P.), calcium phosphate ($Ca_3(PO_4)_2$), a white, tasteless powder almost insoluble in water. Dose, U. S. P., 1 gram; B. P., 0.6 to 2 grams.

CRETA PRÆPARATA (U. S. P.), CRETA (B. P.), prepared chalk, chalk purified by washing and suspension in water ($CaCO_3$). Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

PULVIS CRETÆ COMPOSITUS (U. S. P.), a mixture of prepared chalk, sugar and acacia. Dose, 2 grams.

PULVIS CRETÆ AROMATICUS (B. P.), aromatic chalk powder, contains chalk along with sugar and a number of carminatives belonging to the group of volatile oils. Dose, 0.6 to 4 grams.

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PULVIS CRETÆ AROMATICUS CUM OPIO (B. P.) is a mixture of 39 parts of the aromatic powder with 1 of opium, and therefore contains 2½ per cent of opium. Dose, 0.6 to 4 grams.

MISTURA CRETÆ (U. S. P.), chalk mixture, is compound chalk powder suspended in cinnamon water. Dose, 15 cc.

INJECTIO CALCII GLUCONATIS (U. S. P.), a sterile aqueous solution of calcium gluconate. Dose, 1 gram intramuscularly.

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2. **Barium.**—Barium is the most poisonous of the alkaline earths, but resembles the others in penetrating with difficulty into the epithelium of the alimentary canal, and is therefore absorbed very slowly. It has a characteristic action on many forms of muscular tissue, resembling closely that of veratrine, and the contraction of the frog's muscle under barium is thus stronger than normally, and is greatly prolonged; this action is not opposed by curare and is therefore believed to be exerted on the contractile substance directly. Barium has a somewhat similar action on all forms of muscle. Thus the smooth muscle of nearly every organ is stimulated by barium, *e. g.*, of the gut, bronchi, etc. The frog's heart beats more strongly, but more slowly from a similar action on the muscle fibers, and eventually assumes an irregular peristaltic form of contraction, followed by arrest in systole, as in digitalis poisoning.

In the mammal barium salts injected intravenously cause violent tonic and clonic spasms, from stimulation of the spinal cord and medulla; in sufficient quantities, they finally paralyze the spinal cord. Intravenous injection also provokes the contraction of involuntary muscle in all organs, with vomiting, purging, evacuation of the bladder, etc. The blood-pressure is enormously increased at first, due especially to constriction of the arterioles. In fatal poisoning in animals hemorrhages have been found in the stomach, intestine, kidney and other organs. Intravenous injection of isotonic sodium sulfate has been recommended as an antidote in acute $BaCl_2$ poisoning.

Therapeutic Use.—The soluble barium salts are only used therapeutically in Stokes-Adams syncope. In this condition, barium chloride is given by mouth in doses of 30 mg. three or four times daily, well diluted in water. The dose may be cautiously increased to 40 or 50 mg., four times daily. The results with this drug are, however, not uniformly good.

The principal therapeutic use of barium salts is in roentgenology where the very insoluble, radiopaque barium sulfate which passes through the body unchanged, is used in taking roentgenograms of the gastro-intestinal tract. It may be given by mouth, or in an enema when the colon is to be examined. When used for this purpose, barium sulfate must be very pure, as contamination with more soluble salts such as the chloride or sulfide may make it dangerously toxic.

3. **Strontium.**—Strontium is a comparatively inert substance even when injected directly into the blood, resembling calcium in its action in the body as far as is known, but being even less poisonous. Small doses given intravenously raise the blood-pressure mainly by increased cardiac action, large doses cause

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apnea and death from arrest of the heart (Boriani). It prolongs the contraction of muscle though only to a slight extent. It has not the antagonistic effects to magnesium in the nervous system which are possessed by calcium, but it antagonizes the broncho-dilator action of magnesium. It is absorbed very slowly from the intestine like the other alkaline earths, and is deposited in small quantities in the bones of growing animals, especially when there is a deficiency of lime in the food; but it cannot be used to replace the calcium of the food, animals treated thus showing the symptoms of lime starvation. It is excreted in small quantities by the urine, but mainly by the bowel. Strontium salts have been used to a limited extent in therapeutics, not for the effect of the strontium ion, but for the bromide, iodide or salicylate anions. They possess no advantage over the corresponding salts of potassium and sodium.

4. **Magnesium Salts.**—Magnesium, like calcium, is an indispensable constituent of animal and plant tissues. It is present in the red blood cells and in the tissue cells, particularly in the muscles where it is present in a concentration of about 20 mg. per cent. Magnesium apparently plays a part in many of the enzyme systems of the body, being essential, for example, for the activation of phosphatase, and dephosphorylase. In the plant, it plays the same rôle in the chlorophyll molecule as does iron in hemoglobin. Deprivation of magnesium from the experimental animal leads to vasodilation, hyperirritability of the neuromuscular system, cardiac arrhythmias and ultimately to death. The magnesium salts were shown by Meltzer to have a very powerful action when injected hypodermically or intravenously. The most characteristic effect is complete anesthesia, resembling that induced by the chloroform group, and ending in fatal cases in paralysis of the respiratory center. This arises mainly from direct affection of the central nervous system, and immediate recovery follows the injection of a calcium salt. Higher concentrations of magnesium in the blood have a curare-like action, also antagonized by calcium. The magnesium anesthesia does not appear to arise from its penetrating into the brain cells, for no significant amount can be obtained by analysis, while large quantities are found in the plasma. Applied to a nerve trunk, magnesium salts in 25 per cent solution act in the same way as cocaine, paralyzing first the afferent and later the efferent fibers, and injected into the intradural space they cause complete anesthesia of the lower part of the body like cocaine; magnesium sulfate has, in fact, been employed occasionally for surgical operations and in the treatment of tetanus. The anesthesia lasts much longer and this renders it unsuitable for surgical work, but several cases of tetanus treated by subdural injection of magnesium sulfate have recovered. (Dose, about 0.02 gram per kg. in man.) The same anesthetizing action is seen in the lower invertebrates when a magnesium salt is added to the water in which they live. Magnesium has comparatively little effect on the heart, tending to lessen the excitability of the vagus, and this effect may also be abolished by lime salts. It reduces the irritability of the intestine when injected intravenously and arrests the peristalsis aroused by physostigmine or barium. It also appears to have some effect on the myoneural receptors in muscle, for it arrests the twitchings induced by physostigmine and in large doses interrupts the path from nerve to muscle in the same way as curare.

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It produces curarization of the muscles of crabs, which are unaffected by curare itself. When injected intravenously magnesium produces a fall of blood-pressure mainly due to vasodilatation. The bronchi are dilated in some animals. In small doses magnesium salts cause a reduction, in large doses an increase, in blood sugar. None of these effects is normally elicited when magnesium salts are given by the mouth, as that absorbed is excreted rapidly and there is never enough accumulated in the blood to have any action. Rarely some depression of the nervous system has been observed when very large doses of magnesium sulfate have been given by mouth without producing purgation. Magnesium is excreted by the kidney and traces may appear in the secretions from other organs. It is eliminated rapidly, almost the whole appearing in the urine within forty-eight hours, and this excretion of magnesium is attended by an increase in the calcium of the urine, while that of the feces may diminish.

Therapeutic Uses.—Magnesium sulfate and citrate are used as saline cathartics (p. 239); the oxide and hydroxide, as antacids (p. 80). Magnesium sulfate has also been used as a cholagogue in chronic cholecystitis, and catarrhal jaundice. Because of its action as a depressant of the central nervous system it is used to stop convulsions particularly in children suffering from chronic nephritis and in eclampsia. In children, 0.1 to 0.2 cc. of a 25 per cent solution per kg. of body weight is injected intramuscularly. In the adult the usual dose is 10 cc. of a 25 per cent solution. For more rapid action the injections of a 6 per cent solution may be made intravenously, but following this route of administration the effect is of short duration (one-half hour). The rate of injection must not exceed 3 cc. per minute. Calcium chloride or gluconate for intravenous injection should be on hand to be used as an antidote if respiratory failure follows the parenteral administration of magnesium salts.

Wet compresses of saturated magnesium sulfate are sometimes used for local application to the skin to relieve pain.

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IV. MISCELLANEOUS ANIONS

1. **Phosphates.**—Inorganic phosphorus in the form of phosphate plays an important rôle in the organism, being concerned in the

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deposition of bone, in the regulation of the acid-base balance by the kidney, and as a component of enzyme systems, carbohydrates, fats and other organic constituents of the body with which it forms phosphoric acid esters. The phosphate ion plays the same rôle within the cell as chloride does in the extracellular fluid.

The normal adult requirement for inorganic phosphorus is approximately 1 gram daily but since larger amounts are usually available in the food, phosphate deficiency is not of practical concern. The absorption of phosphate is determined by the calcium content of the food as well as by the acidity of the bowel. About two-thirds of the ingested phosphate is excreted through the urine, the remainder appearing in combination with calcium in the feces.

The sodium and calcium salts of phosphoric acid as well as diluted phosphoric acid are used in therapeutics. Sodium acid phosphate (NaH_2PO_4) is administered in doses of 1 to 2.5 grams every three or four hours to acidify the urine. It is also used as a mild cathartic. Dilute phosphoric acid is used in lead poisoning. Organic phosphates were formerly used as "nerve tonics" but the use of such preparations is neither rational nor of any value.

2. **Oxalates.**—The oxalate ion is highly toxic in large part because of its power of precipitating the calcium of the tissues. Though the oxalates may also cause other effects, this precipitation renders them poisonous to most forms of living matter, of which lime is generally an essential constituent. The oxalate action may be removed in many instances by adding lime salts in excess.

In mammals there is apparently at first a stimulation of the medullary centers, for rapid, deep breathing occurs in the rabbit, and vomiting and nausea in the dog, and according to some observers, the arterial tension is first increased through stimulation of the vasomotor center. Later the movements are wanting in coördination, the respiration becomes slow and dyspneic, the heart is weak, and the animal becomes comatose and dies, sometimes in convulsions.

In cases of oxalate poisoning in man, the early symptoms are great muscular weakness, twitching of the muscles, especially of those of the face, more rarely convulsions; later there follows collapse with a weak, fluttering pulse, pallor or cyanosis, coma and death.

Practically the whole of the oxalate ingested is excreted in the urine in the form of oxalate of calcium, and the insoluble crystals are often deposited along the urinary tubules and may stop them up entirely and thus cause anuria, congestion, and inflammation of the kidney; albuminuria is often the most marked symptom in slight poisoning in man. The deposits of oxalates often form white lines running from the base to the apex of the renal pyramids, which are quite evident macroscopically at the autopsy. Small oxalate calculi have also been produced in the pelvis of the kidney, bladder, or ureter through the prolonged administration of oxalate to animals. Not infrequently these renal changes are the only lesions found postmortem in cases of poisoning with oxalates.

The oxalates are not used in therapeutics but are used in the laboratory as anticoagulants. In cases of oxalate poisoning the natural antidote is

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lime, which forms an insoluble precipitate in the stomach and may also relieve the symptoms induced by the withdrawal of lime from its normal combination in the tissues. At the same time large quantities of water and diuretics may be given in order to wash out the crystals of oxalate from the urinary tubules. Oxalate poisoning has sometimes occurred in man from the use of vegetables containing much oxalic acid, *e. g.*, rhubarb leaves, and from accidental and suicidal poisoning.

The other members of the oxalate series, *malonates* ($CH_2(COONa)_2$) and *succinates* ($(CH_2)_2(COONa)_2$), differ from the oxalates in being much less poisonous, the fatal dose of malonate of sodium being about twenty times that of the oxalate, and the succinate being almost indifferent. The malonate is almost completely oxidized in the tissues, and succinate disappears completely. It is significant that malonic and succinic acids form much more soluble salts with lime than does oxalic acid. Both malonate and succinate of sodium are absorbed only slowly from the intestine, and act as saline cathartics.

3. **Fluorides.**—Fluorine is a normal constituent of the skeleton and is widely distributed in nature. The fluorides, however, are highly toxic being general protoplasmic poisons which like the oxalates precipitate the calcium of the tissues but also act to inhibit many enzyme systems.

In recent years cases of poisoning by sodium fluoride have been described, arising usually from the use of sodium fluoride and sodium fluosilicate (Na_2SiF_6) as insecticides and from its being mistaken for laxative or baking powders. The chief symptoms are nausea, vomiting and diarrhea, accompanied by cramp-like abdominal pains. Clonic convulsions have occurred occasionally and a peculiar gray-blue cyanosis has been observed in some cases. Chronic fluoride poisoning, arising from the use of fluorides in industry, has also been described; giving rise especially to changes in the bones and mottling of the teeth. The latter condition has been observed in communities in which the fluoride content of the drinking water is high. On the other hand, the presence of a certain amount of fluoride in the water and soil is believed to be responsible for the absence of dental caries in the inhabitants of certain localities.

The fluorides absorbed from the alimentary canal are excreted by the urine, but this takes place very slowly, and much of the fluoride is stored up in the body, some in the liver and skin, but most in the bones in the form of calcium fluoride. Crystals of this very insoluble salt are found in masses in the Haversian canals, and increase the hardness and brittleness of the bones.

The fluorides are not used therapeutically but sodium fluoride is used in the laboratory as an anticoagulant and for the preservation of blood.

4. **Sulfides.**—The ordinary sulfides of the alkalies are important only from a toxicological viewpoint. The effect of hydrogen sulfide, apart from its local irritant action, is due to the sulfide which it forms in the blood, and the study of this powerful poison therefore involves a preliminary examination of the effects of the sulfides. Again, sulfur is in itself inert, but is changed to sulfides and hydrosulfuric acid in the

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alimentary canal, and the effects induced by its administration are due to these bodies, and not to the original element (p. 232).

Action.—The sulfides act as irritants in the stomach and bowel, and in the latter induce increased peristalsis and purgation. When injected subcutaneously in the frog, sodium sulfide causes a narcotic condition from depression of the central nervous system, and in sufficient quantities weakens the skeletal muscle and the heart, which continues to beat after complete paralysis has been obtained, but eventually ceases in diastole. After the narcosis has lasted for some time, there follows a marked increase in the reflex irritability, with convulsions resembling those of strychnine poisoning in their general character, but differing from them in lasting continuously for weeks or even months at a time. The animal lies in an extended and tense condition throughout, and passes into complete opisthotonos on being touched.

Sulfides injected intravenously in mammals induce violent convulsions, which seem to be of cerebral origin, for they do not occur in the hind limbs when the spinal cord is cut. The respiration is at first accelerated and later dyspneic and finally ceases, this, along with the paralysis of the vasomotor center, being the cause of death. The heart does not seem to be seriously affected except indirectly through the failure of the respiration and the fall of the blood-pressure.

Sulfide solutions added to drawn blood reduce the oxyhemoglobin at once, and give the blood a dark venous color. At the same time a compound of sulfide and hemoglobin is formed, known as sulfo-hemoglobin or as sulfo-methemoglobin, and gives the blood a greenish color when a thin layer is examined, while a thicker layer is dark red-brown. This sulfo-hemoglobin possesses a characteristic spectrum, marked by a dark line in the red to the left of the D line. Larger quantities give an olive-green color to the blood, and the spectrum of sulfo-hemoglobin disappears. When sulfides are injected into frogs, and more especially when sulfuretted hydrogen is inhaled, the blood gives the characteristic spectrum during life, but this does not seem to be the case in mammals, although sulfo-hemoglobin is formed soon after death. The blood changes are not the cause of death in poisoning, as was formerly supposed, but the direct action of the sulfides on the central nervous system is responsible for their lethal action.

Sulfides absorbed into the blood are rapidly oxidized, and are excreted in the urine in the form of sulfates and of organic sulfur compounds of unknown constitution. Small quantities escape by the lungs, and give the breath the disagreeable odor of sulfuretted hydrogen, and some is excreted in this form in the perspiration.

The sulfides dissolve the horny epidermis and hair very readily when they are applied to the skin. If the application is continued, some irritation and redness is produced.

Hydrosulfuric Acid (sulfuretted hydrogen, hydrogen sulfide (H_2S)) is a gas with strong irritant properties, which it shares with other acids (see page 86) and has not infrequently given rise to poisoning, as it is formed in large quantities in the course of the putrefaction of sulfur compounds such as proteins. Sewer gas often contains it in quantity, and workmen employed in cleansing sewers or cesspools have often suffered from its effects. When inhaled in concentrated form it is almost immediately fatal, the patient losing consciousness at once, and the respiration ceasing after a few seconds. In smaller quantities it causes immediate unconsciousness, lasting for several hours and then passing into fatal coma, which is often interrupted by violent convulsions. In both of these forms the symptoms are due to the direct action of the sulfides on the brain and medulla oblongata. Persons exposed to a very dilute vapor of sulfuretted hydrogen suffer from local irritation of the eyes, nose and throat, indicated by pain and congestion of the conjunctiva, sneezing, dryness and soreness of the mouth and throat, and a reflex increase in the secretion of tears, saliva, and mucus. Headache, dulness, giddiness, and loss of energy are complained of; the symptoms frequently appear only some time after the exposure to the poison. Death in animals exposed to these dilute fumes is due in part to edema

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of the lungs caused by the local irritant action. One part of hydrosulfuric acid in 5,000 of air is sufficient to induce symptoms in man, and an atmosphere containing one part in 2,000 can be respired for only a short time, and gives rise to alarming symptoms; about one part of hydrosulfuric acid in 1,000 parts of air is sufficient to poison a man fatally in ten minutes.

The poisonous effect of sulfuretted hydrogen is due in part to its local irritant action, in part to its directly affecting the central nervous system. The changes in the blood occur during life only after very concentrated gas is inhaled, although they may indicate the poison after death from more dilute vapor, for the tissues in general tend to assume a green color sooner after hydrosulfuric acid poisoning than in the course of ordinary putrefaction.

Hydrogen sulfide is destructive to most forms of life, even when present in comparatively small amount. The microbes of putrefaction, which produce it themselves, are eventually killed by this gas, unless it escapes freely.

Preparations

Potassa Sulfurata (U. S. P.), Potassa Sulphurata (B. P.), liver of sulfur (Hepar Sulphuris), is a mixture of polysulfides and thiosulfides, often containing sulfate of potassium; irregular brownish or greenish pieces soluble in water and possessing an unpleasant saline taste, and an odor of hydrogen sulfide.

Sulfurated potassium is used to a very limited extent as an external application in certain skin diseases, particularly in acne, and to destroy skin parasites, such as that of scabies. It is used as an ointment (1 part to 10 parts) and is somewhat irritant.

Sulfides, especially barium sulfide, are used occasionally to remove hair. They cause destruction of the hairs but not of the follicles, so that the hair continues to grow.

5. **Iodides and Iodine.**—Iodine and the iodides resemble one another in many of their general systemic effects and hence may be considered together. Although the iodides have been more largely used in medicine than any of the other salts of the alkalies, their mode of action is still in many ways obscure. In addition to their therapeutic activity the iodides and iodine give rise to symptoms of poisoning which vary considerably not only in different individuals, but also in the same person at different times.

Symptoms.—Large quantities of the iodides cause irritation of the stomach from their salt-action and induce nausea and vomiting, more rarely diarrhea; but these symptoms are quite distinct from those known as **Iodism,** which may arise from comparatively small quantities, and which are most commonly seen when either the iodides or iodine have been administered repeatedly.

The commonest symptom of iodism is catarrh of the **Respiratory Passages,** more especially of the nose, which betrays itself in some swelling and discomfort in the nasal mucous membrane, in a profuse water secretion, and in sneezing. The catarrh spreads upward to the conjunctiva, which often becomes swollen and congested. There may be marked lacrimation and edema of the eyelids. The frontal sinuses are involved, inducing a feeling of dulness or violent headache; and the condition may progress downward to the tonsils, which become swollen and inflamed in some cases. Still lower it occasionally causes some swelling and edema or small ulcers in the larynx, and has thus caused dyspnea, which has necessitated tracheotomy, or very rarely has proved fatal. Bronchitis has also been observed in man, with a profuse watery

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secretion, and in animals edema of the lungs and pleuritic effusion have been produced by the injection of iodides. Even small quantities injected intravenously increase the mucus secreted by the bronchi.

In the **Mouth** iodism is often betrayed by swelling and irritation of the throat and tonsils and by salivation, rarely by swelling of the salivary glands. The stomach is seldom affected, the appetite generally remaining good, but in some persons iodides induce nausea and gastric discomfort. A single dose of iodide increases the amount of gastric juice and prolongs the secretion aroused by the taste of food.

Skin Eruptions of different forms are also common results of the administration of iodides, but are less liable to occur in the beginning of the treatment than the catarrh of the respiratory passages. These eruptions may simulate almost all known skin diseases, but the most common forms are erythematous patches, or papular eruptions, which may pass into pustules or into larger inflamed areas. Eczema, bullæ, pemphigus and purpura arise less frequently from the use of iodides. In some cases a more or less defined area of edema has been observed in the face, especially around the eyes.

The **Secretion of Urine** is generally increased by the administration of iodides, as of other salts of the alkalies, though they seem to have no specific action on the kidneys. In rare cases albuminuria has been observed, and some irritation of the bladder, urethra and vagina is said to have been induced by iodide treatment.

In many instances small doses of iodide or iodine may be given repeatedly without any noticeable disturbance, but in others the smallest quantity (0.2 gram) induces severe poisoning. Some authorities consider that these small doses are more liable to cause iodism than larger ones, but the action of the drug is so capricious that the statistics of different observers show great discrepancies, even when approximately the same dose has been given.

Among other conditions which favor the onset of symptoms is a slow excretion of the iodide such as is observed in some forms of renal irritation. Children seem less liable to suffer from the iodides than adults. The dose administered has, of course, some relation to the onset of symptoms; thus, very large doses are more likely to induce them than very small ones, but it seems that a tolerance is soon established in some cases, for after iodism has been induced, and the daily dose lessened accordingly, it is sometimes found that it may be gradually increased until a quantity considerably greater than that originally given may be taken with impunity. In other instances, a definite quantity may be given for a long time without inducing symptoms, but these may suddenly set in without any apparent change in the treatment and without any appreciable cause. Very often it is found that the symptoms disappear while the treatment is continued, and recovery invariably sets in when the drug is abandoned. The iodides all induce iodism, the symptoms being apparently unaffected by the basic ion. The condition is seldom dangerous, but a few cases are recorded in which edema of the larynx resulted and proved fatal.

The iodides are not **Absorbed** from watery solutions applied to the

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skin, but are rapidly taken up by all the mucous membranes. When given by the mouth they are absorbed unchanged by the intestine, and appear in the secretions within five to ten minutes. The greater part of the iodide is **Excreted** in the urine, in which it appears as salts. Some escapes by the salivary glands, however, and small quantities are excreted by the stomach as hydriodic acid, from which free iodine may

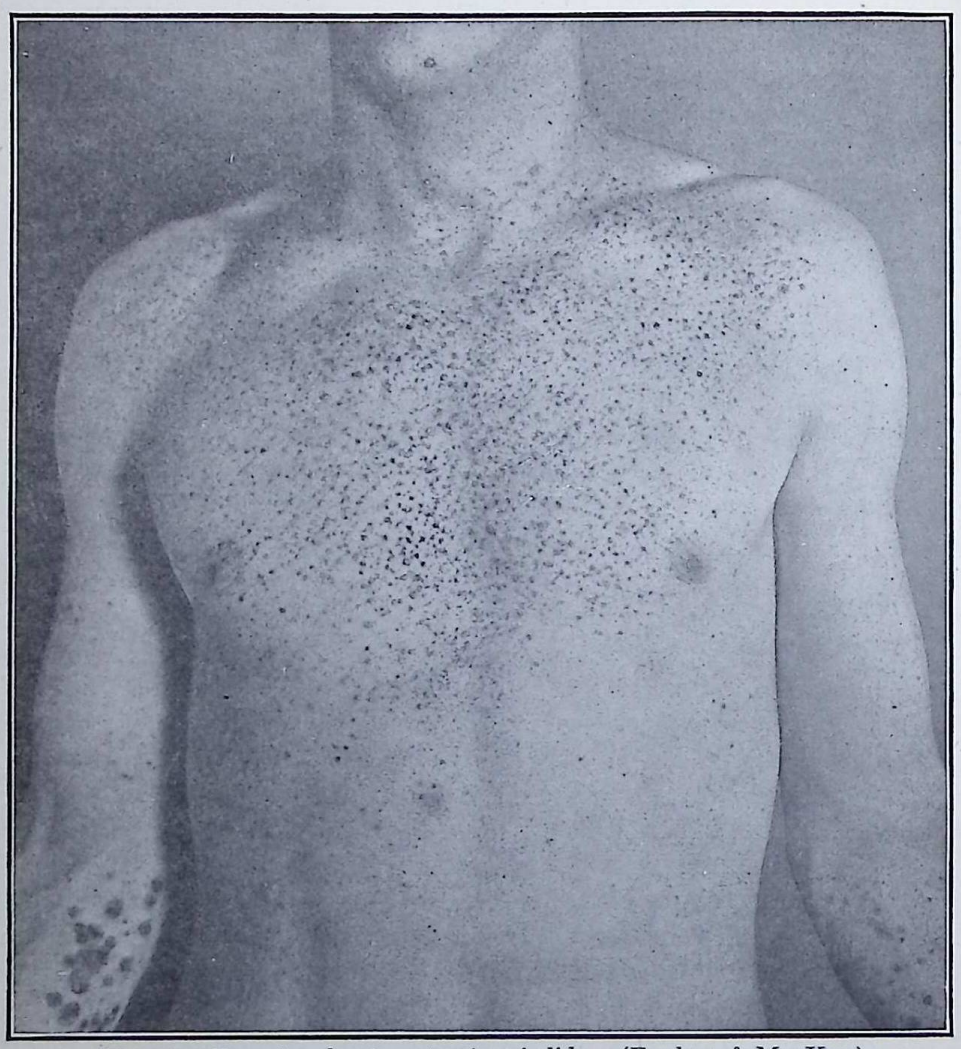

FIG. 3.—Eruption due to potassium iodide. (Fordyce & MacKee.)

be formed; iodide has also been found in the tears, perspiration, milk. sebum, and in the secretion of the nasal mucous membranes.

Iodides are much more rapidly excreted than bromides, for 65 to 80 per cent of the iodide appears in the urine within twenty-four hours after its administration, and no iodide reaction is obtained from any of the secretions a week after the treatment has ceased.

Iodine possesses a local irritant action similar to, though less intense than, that of chlorine and bromine (p. 799). It is much less volatile, and therefore comes into contact with the tissues more slowly than

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these, but the chemical change is analogous, and iodides and iodo-protein compounds result.

Action.—When applied to the **Skin**, it dyes it a yellow-brown or dark brown color, and acts as an irritant, producing a sensation of heat and itching. In very concentrated solution or in the solid form it may cause blistering or even corrosion, but it acts more slowly than most other irritants, and at the same time the irritation is more prolonged. It penetrates into the deeper layers of the skin, and small quantities are absorbed.

The **Mucous Membranes** are more strongly affected by contact with it; thus when its vapor is inhaled for some time, smarting, swelling and increased secretion are caused in the nasal mucous membranes, conjunctiva, throat and lower respiratory passages, resembling exactly the symptoms known as iodism. In the stomach small quantities may cause slight irritation and improved appetite, but as a general rule nausea, discomfort and vomiting follow its administration in any save minute doses, and occasionally diarrhea has been observed after it from irritation of the bowel. In cases of poisoning, the irritation of the alimentary canal may prove fatal by inducing collapse and failure of the heart and respiration, and iodine may be recognized in the vomited matter and in the stools.

Solutions of iodine **Injected Subcutaneously** or into tumors or cysts, formerly a common method of treatment, cause intense pain and irritation, which may induce collapse and which have been followed in some instances by suppuration and gangrene.

Iodine is **Absorbed** in the form of iodides, and perhaps in combination with proteins. Its fate in the body is precisely similar to that of the iodides—it is excreted in the form of iodides, chiefly by the kidneys, to a less extent in the saliva, perspiration, milk and secretions of the respiratory passages. The administration of iodine leads to an increase in the iodine of the thyroid gland.

Small quantities of iodine may be given internally to many persons without eliciting any symptoms except those which are clearly due to the local action. Repeated doses, however, sometimes cause symptoms resembling those observed after iodides (**Iodism**), although these have been much less often induced by iodine.

The **thyroid gland** is particularly concerned with the metabolism of iodine, which is a constituent of the thyroid hormone (*cf.* p. 540). When iodide is injected a large part is removed from the circulation by the thyroid which has a special affinity for this element. In the normal animal the administration of iodides causes a stimulation of the thyroid as evidenced by the histological appearance of the cells, but this stimulation gives rise to no obvious symptoms. On the other hand, in certain cases of adenoma of the thyroid, the administration of iodine may induce thyrotoxicosis with the appearance of symptoms due to hyperthyroidism. In Graves' disease (exophthalmic goiter) on the other hand, the administration of iodine reduces the activity of the gland, and leads to a remission of the symptoms of hyperthyroidism. This suppression of thyroid activity is probably an indirect one and not due to the direct action of iodide on the gland, as was formerly believed.

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Therapeutic Uses.—The iodides prior to the introduction of penicillin were used very extensively in the treatment of tertiary *syphilis*. In syphilitic bone disease and ulcers, and in the gummata of the brain and other internal organs, a remarkable improvement very often occurs after the iodide treatment has been adopted. The iodide of potassium or of sodium is almost invariably used, and is often given in large doses, up to 5 grams daily. The iodide is often prescribed along with mercury, and this combination is found more efficient than the iodide alone. In actinomycosis, iodide treatment has proved of value, and was the drug of choice until the advent of penicillin. In a rare infection known as sporotrichosis, which arises from a fungus nearly related to actinomyces, as well as in other fungus infections, the iodides have also proved of value.

In *syphilis* and in these other diseases, the iodide does not act as a parasiticide; the spirochete of syphilis, for example, is not killed by the application of iodide of potassium to a syphilitic lesion, and the fungus of sporotrichosis grows readily in a culture medium containing high concentrations of iodide. The specific effects of iodide in tertiary syphilis are exerted not on the parasite but upon the tissues in which it lives and which have reacted to its presence by the formation of gummatous tissue; these granulomatous tissues dissolve under the action of iodides, while the parasite remains unaffected, but is now more readily accessible to the parasiticide drugs, mercury and arsenic. It is important to recognize that iodide does not destroy the cause of the infection but only removes some of the results.

An important therapeutic use of iodine and the iodides is in the treatment of certain diseases of the thyroid. Where the available iodine in the food is deficient, which is the case particularly in certain mountainous areas and the great plains, there is a tendency for the thyroid gland to enlarge and form a goiter. In such goitrous areas the administration of iodine in the form of iodized salt (in which a small amount of iodide is added to the table salt) prevents the deficiency of iodine and goiter is eliminated. Iodine may also be administered to the children in goitrous areas in doses of 0.2 gram each during ten days twice a year. During pregnancy likewise, where the demand for iodine is increased, the administration of small amounts prophylactically is desirable. The use of iodine as just outlined has greatly reduced the incidence of colloid goiter and cretinism in goitrous areas.

Another important use of iodine and the iodides is in Graves' disease (exophthalmic goiter). The preoperative use of iodine in the form of Lugol's solution in cases of exophthalmic goiter produces histological changes in the thyroid gland which are quite remarkable. The epithelial hypertrophy resolves into the appearance of normal acinar epithelium, colloid appears in abundance, although it is rather thin and watery. The hyperplasia of the primitive lymph follicles, on the contrary, seems to be increased. If the treatment is extended over a period greater than that of ten days or two weeks the amount of thin, watery colloid increases and a certain degree of enlargement of the acinar cells with lipid and

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vacuolar degeneration results, accompanied by marked lymphoid hyperplasia.

Iodine, usually in the form of Lugol's solution, is used before operations for exophthalmic goiter and the discovery of its value has done much to decrease the dangers associated with the surgical treatment of this condition. It is usually administered in milk in doses of about 10 minims three times a day after meals. The patients improve rapidly under its effects—the nervousness lessens, sleep and appetite improve, the heart becomes slower and the basal metabolism decreases. The patient is protected against post-operative crisis. The drug is not by any means a cure for the disease but is only to be regarded as a temporary measure to prepare a patient for the surgical treatment of the condition. The beneficial effects usually reach their maximum between ten days and three weeks after the drug is started and operation is best done during this period. Following the operation the administration of the iodine is usually continued for a few days.

Radioactive iodine has also been used recently in the treatment of Graves' disease. Since iodine is concentrated in the thyroid gland, the radiations induce the same destructive effects on the tissue as are obtained by external irradiation. The temporary remission induced by the iodine is, therefore, followed by a permanent remission.

Iodides are often prescribed along with other remedies in *expectorant* mixtures, the object being to render the bronchial mucus more watery and less tenacious, and thus to facilitate its removal. In some cases of asthma they have been found of value, perhaps from the same action, for they do not appear to affect the bronchial muscle.

Iodine is applied **locally** by painting on the skin in a variety of chronic inflammatory processes, such as tuberculous glands, pleuritic effusion, and tuberculous or rheumatic joint disease. Its action here consists simply of a mild lasting irritation of the skin, which induces some congestion in the subcutaneous tissues and may thus aid in the absorption of exudates in them and may also influence the deeper lying tissues and organs in the same way as other irritants (see p. 197). There is, however, nothing specific in its action, and it differs from the other skin irritants only in being milder in action and more enduring in its effects. It seems unlikely that the small quantity absorbed can have any appreciable action. Some benefit often follows from this use of iodine in chronic inflammations, but there is no question that it is very often applied where more active surgical measures are really required.

Iodine was formerly injected into cysts in order to induce inflammation and adhesion of their walls, and thus to obliterate the cavity. It is used extensively to disinfect the skin before operation (see p. 796).

Iodide of potassium is sometimes added to other drugs in cases of *malingering*, or in which it is suspected that the patient is not taking the remedy as directed. If the iodide is swallowed it can be detected in the urine by the addition of a few drops of chlorine water and of starch solution, which assumes the well-known blue color.

Iodides have to be used with care in cases of pulmonary phthisis, in which they often increase the cough and expectoration, and in some

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cases, it is alleged, cause hemoptysis and promote the infection of fresh tissue. If the tuberculous nodule is broken down by the iodides in the same way as the gumma, the bacillus may be freed, and many clinicians deprecate the use of iodide in all forms of tuberculosis. Children have sometimes been found to suffer from iodism from being nursed by a person under iodide treatment.

Iodism very often proves a disagreeable accompaniment of the treatment, and is sometimes so severe as to preclude the use of the salts, so that many attempts have been made to discover some expedient by which these symptoms may be avoided, but as yet no success has been obtained.

ORGANIC IODINE COMPOUNDS FOR SYSTEMIC USE

A number of iodine compounds with proteins and fats have been introduced as substitutes for the inorganic iodides. These are less irritating to the digestive tract but like the inorganic derivatives may also induce the symptoms of iodism when used in therapeutically effective doses. Employed in the dosages ordinarily advocated, the organic iodides are weaker than full doses of the inorganic forms. Among the iodized fats and fatty acids are oridine, the calcium salt of the iodized fatty acids of cottonseed oil, riodine, iodinated castor oil, and calcium iodobehenate (sajodin).

PREPARATIONS OF IODINE USED FOR DIAGNOSTIC PURPOSES

In recent years iodine and certain other roentgen-ray opaque substances have been introduced into medical practice as an aid to diagnosis. They have been used, for instance, as an aid to diagnosis in pathological conditions in the lungs, in suspected disease of the gall bladder and the genito-urinary tract, and in the visualization of the blood vessels and spinal canal. Several preparations are in use at the present time, those containing iodine being discussed here while the phthalein compounds used especially to permit visualization of the gall bladder will be mentioned elsewhere.

In pulmonary conditions other than those due to tuberculosis, iodized oils are sometimes employed. *Oleum Iodatum* (U. S. P.) (lipiodol) contains about 40 per cent of iodine in organic combination with poppy-seed oil. After the pharynx and base of the tongue have been anesthetized, the oil may be administered by dropping it through the glottis as the patient inspires, or it may be injected into the trachea by means of a curved cannula inserted between the cocainized vocal cords. It may be given also through a bronchoscope. More commonly it is given through a curved cannula inserted through the cricothyroid membrane, the required amount being injected into the anesthetized trachea, roentgenograms being taken immediately after the injection has been completed. Usually no symptoms follow immediately upon the administration of the oil, but in about fifteen minutes coughing may occur with ejection of most of it. The oil which is retained usually disappears in a week or two but it may be retained in the lungs for a considerable

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period. Iodism rarely follows from this use of iodized oil unless some of the oil is swallowed, when symptoms may occur.

A 10 per cent iodized poppy-seed oil (lipiodol radiologique ascendant) is also available for use in the recognition of intradural tumors where it is desired to employ a contrast medium of lesser density than that of the spinal fluid. The introduction of iodized oils into the subarachnoid space may induce leptomeningeal irritation and hence these compounds should not be employed unless absolutely unavoidable.

WATER-SOLUBLE ORGANIC IODINE COMPOUNDS FOR ROENTGENOGRAPHY

Designation	*Chemical structure*	*Iodine content per cent*
Diodrast	Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid	50
Diodrast concentrated solution	Diethylamine salt of 3,5-diiodo-4-pyridone-N-acetic acid	
Diodrast compound solution	A mixture of the above two compounds	25
Hippuran	Sodium ortho-iodohippurate	39
Neo-iopax (iodoxylum)	Disodium N-methyl-3,5-diiodo-4-pyridoxyl-2,6-dicarboxylate	52
Skiodan (methiodal)	Sodium mono-iodo-methanesulfonate	52

For renal pyelography and the visualization of the blood vessels, water-soluble organic iodine compounds are injected intra-arterially and intravenously (excretory urography) or introduced through the ureters (retrograde pyelography). The intravenous use of these drugs is contraindicated in patients with liver disorders, nephritis or severe uremia and they must be used cautiously in cases of tuberculosis and hyperthyroidism. The compounds used for this purpose are given in the accompanying table. Diodrast, diodrast compound solution, hippuran and neo-iopax are all used for renal pyelography. Hippuran may also be administered orally for this purpose. Diodrast concentrated solution is used for the visualization of the heart and large vessels.

The parenteral administration of any of these organic iodine compounds is sometimes accompanied by untoward reactions and fatalities have occasionally been observed following their use. In patients with a history of allergy in whom a reaction or idiosyncrasy to iodine is suspected, a small initial dose should be given first. Epinephrine hydrochloride should be available to be used in case of a reaction.

PREPARATIONS

IODUM, iodine (U. S. P., B. P.), grayish-black plates, with a metallic luster and a characteristic odor. Soluble about 1 in 3000 of water, 1 in 12 alcohol, freely in chloroform; is dissolved by aqueous solutions of iodides.

POTASSII IODIDUM (KI), and SODII IODIDUM (NaI), (U. S. P., B. P.), colorless crystals, very soluble in water. Dose, 0.3 to 2 grams.

CALCII IODOBEHENAS (U. S. P.) $(C_{21}H_{42}ICOO)_2Ca$, a white or yellowish powder, insoluble in water. Dose, 0.5 gram.

LIQUOR IODI, solution of iodine (U. S. P.), contains 2 per cent of I and 2.4 per cent of NaI in water.

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IODOXYLUM (B. P.), iodoxyl, the disodium salt of N-methyl-3:5-diiodo-4-pyridone-2:6-dicarboxylic acid. Dose, 10 to 15 grams intravenously.

LIQUOR IODI AQUOSUS (B. P.), aqueous solution of iodine, lugol's solution, liquor iodi compositus, an aqueous solution of iodine (5 per cent) and potassium iodide (10 per cent). Dose, 0.3 to 1 mil.

LIQUOR IODI FORTIS, strong solution of iodine (U. S. P.), contains 5 per cent of I and 10 per cent of KI in water. Dose, 0.3 cc.

LIQUOR IODI FORTIS (B. P.), contains 10 per cent of I and 6 per cent of KI in 90 per cent alcohol.

LIQUOR IODI MITIS, weak solution of iodine, weak tincture of iodine (B. P.). Contains 2.5 per cent of iodine, 1.5 per cent of potassium iodide in 90 per cent alcohol. Dose, 0.3 to 2 mils.

LIQUOR IODI SIMPLEX, simple solution of iodine (B. P.), contains 9 per cent of iodine in 95 per cent alcohol. Dose, 0.2 to 1 mil.

OLEUM IODATUM (U. S. P.), an iodine addition product of vegetable oils containing about 40 per cent of organically combined iodine.

OLEUM IODISATUM (B. P.), iodised poppy-seed oil containing 39 to 41 per cent of combined iodine.

SYRUPUS FERRI IODIDI, syrup of ferrous iodide (B. P.), contains 5 per cent of FeI_2 and 1 per cent of dilute hypophosphorous acid in aqueous syrup. Dose, 2 to 8 mils.

TINCTURA IODI, tincture of iodine (U. S. P.), contains about 7 per cent of I and 5 per cent of KI in 90 per cent alcohol.

TINCTURA IODI MITIS, mild tincture of iodine (U. S. P.), contains about 2 per cent of I and 2.4 per cent of KI in about 50 per cent aqueous alcohol.

UNGUENTUM IODI, iodine ointment (U. S. P.), 4 per cent of I, 4 per cent KI and 12 per cent glycerin in yellow ointment.

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V. ALKALIES

1. **Hydrates and Carbonates of the Fixed Alkalies.**—The hydrates and carbonates of potassium, sodium and lithium owe their pharmacological action entirely to the non-metallic ion, which is so much more powerful than the metal that the latter may be discounted.

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Applied to the **Skin**, weak solutions dissolve the superficial layer of horny matter and the oily secretions of the glands, and thus cleanse the surface more thoroughly than water or solutions of neutral salts. When applied for some time, they penetrate more deeply and cause some slight irritation and redness. Concentrated solutions dissolve the skin and cause necrosis of the deeper tissues, generally covered by a semitransparent crust which falls off in the course of a few days, leaving an ulcer. The solutions of the carbonates are much less corrosive than those of the hydrates, and induce actual lesion of the skin only under exceptional circumstances, such as very prolonged application.

In the **Mouth** the hydrates and carbonates have a characteristic "alkaline" taste, and dissolve the superficial layers of the lining membrane and the mucus of the secretions. The lips, tongue, and gums assume a bright red color from the irritation and feel soapy to the touch. Concentrated solutions may cause deep corrosion, as in the skin, while very weak solutions have no effect except the characteristic taste and a reflex flow of saliva. The corrosion caused by strong solutions extends to the throat and esophagus, and may either prove immediately fatal or may subsequently give rise to cicatrices.

The effect of the hydrates and carbonates in the **Stomach** varies according to the dose given and the state of digestion at the time. They act chiefly in two ways, by directly modifying the reaction of the stomach contents, and, secondarily, by affecting the pyloric reflexes. Small quantities are undoubtedly neutralized by the hydrochloric acid of the gastric juice and act no longer from their alkalinity, but merely from their effects as salts, if at all. Larger quantities render the contents of the stomach neutral or alkaline and thus prevent gastric digestion. Very concentrated solutions corrode the walls of the stomach and may prove immediately fatal from causing perforation into the peritoneal cavity, while if the corrosion is not so severe, and the patient recovers from the shock and collapse, gastric ulcer and cicatrices may result.

In hyperacidity of the stomach, the alkalies may be of benefit by lessening the amount of free acid present. Dilute solutions of the alkalies may act as slight irritants to the stomach wall and thus improve its circulation, and lessen pain, eructation and distention, very much in the same way as other slight gastric irritants, such as the volatile oils. In the case of the carbonates and bicarbonates, this carminative action may be strengthened by the carbonic acid liberated by the hydrochloric acid. In addition, they tend to render the mucus less tenacious, or may dissolve it completely, and thus improve the condition of the stomach.

The movements of the stomach are not much affected by the reaction of its contents until these pass into the duodenum. An excessive acidity or alkalinity of the gastric contents entering the duodenum tends reflexly to cause spasmodic contraction of the pyloric sphincter. Alkalies tend to hasten the emptying of the stomach if they alter the reaction in the direction of neutrality, that is especially in cases of hyperacidity.

In the small **Intestine** the alkalies have been shown to have an indirect effect, through their diminishing the acidity of the gastric juice. The secretion of the pancreas is normally augmented on the passage of an

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acid fluid through the pylorus, and if the acidity of this fluid be reduced by the administration of alkalies, a smaller quantity of pancreatic juice is thrown into the intestine. This may again render the digestion less complete, although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted.

Absorption.—Following its neutralization in the stomach, sodium bicarbonate is converted to sodium chloride which is absorbed from the intestine. Any excess alkali not neutralized is also absorbed. The total base of the body is increased by an amount equivalent to the sodium bicarbonate ingested for even when the alkali administered has been neutralized by the gastric juice, the reserve of available alkali is augmented.

The organism rapidly frees itself from the excess of alkali by **Excreting** alkaline salts. This excretion occurs chiefly in the urine, which becomes less acid, or even alkaline in reaction, and in the latter event contains bicarbonate of potassium or sodium. As a general rule, the urine soon regains its acidity, but when fairly large doses are given repeatedly, its reaction may be kept alkaline constantly. This is almost always accomplished in man by the administration of about 10 to 15 grams of sodium bicarbonate in twenty-four hours, but some persons require a still larger quantity, while others require less. A temporary alkaline reaction lasting two to three hours may be induced by a single dose of 2 to 3 grams. The alkalies have the same effect on the excretion of the salts in the urine as the neutral salts; large doses increase the sodium, potassium, and chlorides of the urine.

Therapeutic Uses.—The caustic alkalies are used **Externally** to a limited extent to remove growths, such as warts, from the skin. For this purpose the potash pencils are employed, but they are very deliquescent and it is therefore difficult to limit their action to one spot, and to the superficial tissues. When the desired extent of cauterization has been obtained, the part should be washed with water, or with vinegar or some other dilute acid. The carbonates are also used externally to some extent, chiefly in baths, which they render more irritant to the skin, and in which they tend to soften and remove the superficial horny layers of the epithelium more than ordinary water or solutions of the neutral salts. The carbonates are also applied in strong solution or as a paste in itching skin diseases, and often give relief.

Internally sodium bicarbonate is used for its effect on the *stomach*, and in cases of hyperacidity relieves the pain and eructation almost instantly. As the concentration of the acid secreted by the stomach seems to be fairly constant, the acidity of the stomach depends upon the relation between the quantity of the secretion and the volume and nature of the stomach contents. Normally the acidity rises to a maximum about one hour and a half after a meal and then declines rapidly; but in *hyperchlorhydria* the acidity may remain high for hours. In this condition alkalies are usually given after meals. Sodium bicarbonate is frequently used for this purpose because of its ready availability (as baking soda) and inclusion in many proprietary preparations. It exerts a rapid action but the duration of its effect is brief and its continued

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administration may lead to symptoms of alkalosis. These are manifested by mild gastric complaints, anorexia, nausea, and when severe by nervous and neuromuscular manifestations. The carbon dioxide combining power of the blood is increased (80 to 100 volumes per cent), the serum chlorides decreased, and renal function becomes impaired.

In view of the undesirable effects which follow the use of sodium bicarbonate as an antacid, it has been displaced for this purpose by the oxides, hydroxides and carbonates of the alkali earth metals (calcium, magnesium, aluminum) which are not absorbed and hence exert no systemic effects.

The proportionate amounts of the more commonly used antacids necessary to neutralize a given quantity of hydrochloric acid were found by Clark to be as follows: magnesium oxide, 3; magnesium carbonate, 7; calcium carbonate, 7; sodium bicarbonate, 12; bismuth subcarbonate, 136. Weight for weight, therefore, magnesium oxide has a four-fold greater antacid effect than sodium bicarbonate, while bismuth subcarbonate has a relatively feeble effect in this direction. When magnesium oxide is used as a stomach antacid, the resulting magnesium chloride acts as a mild purgative, whereas if calcium carbonate be used the calcium chloride formed acts as a mild astringent. In the treatment of hyperacidity or of gastric ulcer, disturbance of intestinal functions can be prevented by alternating magnesium oxide and calcium carbonate or by other combinations of antacids. Tribasic magnesium phosphate is also used as an antacid with the intention that, while it is a moderately effective antacid, it does not produce systemic alkalosis. Magnesium trisilicate has antacid and adsorbent properties useful in the treatment of gastric ulcer and gastritis. Its neutralizing action continues for several hours and it does not cause alkalosis or toxic symptoms even in large doses. Aluminum hydroxide has also been used widely in recent years in the treatment of gastric ulcer. It is used in the form of a colloidal suspension. In the Sippy treatment for gastric ulcer, mixtures of 0.6 gram each of magnesium oxide and sodium bicarbonate are alternately administered with a mixture of 0.6 gram of bismuth subcarbonate and 2 to 3 grams of sodium bicarbonate. Even where no excessive acidity exists, the alkalies are often beneficial in small quantities, removing distention and discomfort without apparently altering the digestion to any marked extent. The bicarbonate of potassium is frequently used for this purpose but there is no reason to believe that it is more effective than the cheaper sodium salt. Whatever preparation is used, it ought to be well diluted to avoid the irritant action on the stomach wall. When the secretion does not seem to contain an excessive amount of acid, they are advised before meals, and may then be combined with other stomachics, such as bitters or volatile oils.

The alkaline preparations are also largely used for their effects on the urine. The acetates, citrates, etc., may also be used for this purpose since they are converted to sodium bicarbonate in the body and hence exert the same ultimate effect as this salt. In cases of *excessive acidity of the urine*, leading to pain and straining during micturition, the symp-

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toms are relieved by these drugs rendering the fluid less irritating, and this relief is especially marked in irritated conditions of the bladder and urethra. They may also be of value in those cases by rendering the mucus more soluble in the bladder. In the acute stage of *pyelitis* and *cystitis*, especially when due to Bacillus coli infection and when the acidity of the urine is high, the symptoms may be relieved by keeping the urine temporarily alkaline by administration of sodium bicarbonate or of potassium citrate. In *gravel*, the alkalies also give relief, and this has been attributed to their dissolving the uric acid in the urine, or rather to their keeping it in solution in the form of salts. In order to attain this, the urine would have to be rendered alkaline, or at least neutral, and relief is given by quantities of the alkalies which are quite insufficient to do this; this relief in gravel results from the amount of the urine being increased while its acidity is lessened; the inflamed surface of the bladder is thus bathed in a less irritant fluid and the pain is diminished.

In the presence of cystine, uric acid, or xanthine stones it is desirable to maintain the urine on the alkaline side so as not to favor the deposition of these substances. On the other hand, in phosphate and carbonate calculi, an alkaline urine is to be avoided since these are precipitated under these conditions.

Sodium bicarbonate is frequently administered in doses of 2 to 3 grams concurrently with other drugs in order to alkalinize the urine and prevent the deposition of insoluble materials. Thus in the treatment of gout with the salicylates or neocincophen it is given to prevent the deposition of uric acid in the kidney. Likewise when the sulfonamides are used, sodium bicarbonate or other absorbable systemic alkali therapy should be used to prevent the deposition of these drugs in the urinary tract.

The bicarbonate of potassium is often added to other *expectorant* remedies in the treatment of bronchial catarrh and bronchitis, and is believed to increase the excretion and render it more fluid and more easily expectorated.

The alkaline carbonates may be given as antidotes in poisoning with the corrosive acids, although magnesia is preferable, because it is less irritating to the stomach. Alkaline solutions should not be injected hypodermically, as sloughing has been observed repeatedly from this procedure.

In cases of **Poisoning** with the caustic alkalies, the treatment consists in the administration of dilute acids, of which the organic—acetic, citric or tartaric—are the best. The first is most readily obtained in the form of vinegar. No attempt should be made to pass the stomach tube, as it is liable to pass through the corroded wall of the esophagus or stomach. General measures, such as central nervous stimulants, warmth, etc., may be taken.

The symptoms of alkalosis resulting from the ingestion of large amounts of alkali, as mentioned above, disappear when the alkalies are withdrawn. In cases of severe alkalosis the administration of acidifying salts (calcium chloride, ammonium chloride) may be necessary.

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PREPARATIONS

MAGMA MAGNESIÆ (U. S. P.), milk of magnesia, a suspension of magnesium hydroxide in water containing about 8 per cent of $Mg(OH)_2$. Dose, as antacid, 4 cc.; as laxative 15 cc.

MAGNESII CARBONAS (U. S. P.), a white insoluble powder. Dose, as antacid 0.6 gram; as laxative, 8 grams.

MAGNESII CARBONAS LEVIS (B. P.), light magnesium carbonate. Dose, 0.6 to 4 grams.

MAGNESII CARBONAS PONDEROSUS (B. P.), heavy magnesium carbonate. Dose, 0.6 to 4 grams.

MAGNESII OXIDUM (U. S. P.), magnesia (MgO), a white powder. Dose, as antacid 0.25 gram; as laxative, 4 grams.

MAGNESII OXIDUM LEVE (B. P.), light magnesium oxide. Dose 0.6 to 4 grams.

MAGNESII OXIDUM PONDEROSUM (U. S. P., B. P.), heavy magnesium oxide (MgO) (U. S. P.), a dense white insoluble powder. Dose, U. S. P., as antacid, 0.25 gram; as laxative, 4 grams; B. P., 0.6 to 4 grams.

MAGNESII PHOSPHAS TRIBASICUS (U. S. P.), $Mg_3(PO_4)_2.5\ H_2O$. Dose, 1 gram.

MAGNESII TRISILICAS (U. S. P., B. P.), magnesium trisilicate ($2MgO.3\ SiO_2nH_2O$), a fine white tasteless powder almost insoluble in water. Dose, U. S. P., 1 gram; B. P., 0.3 to 2 grams.

MISTURA MAGNESII HYDROXIDI (B. P.), cream of magnesia, a suspension of magnesium hydroxide in water containing 8.25 per cent of $Mg(OH)_2$. Dose, 4 to 16 mils.

POTASSII BICARBONAS (U. S. P., B. P.) ($KHCO_3$), colorless, transparent crystals with a saline, slightly alkaline taste and soluble in 4 parts of water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

POTASSII CARBONAS (U. S. P., B. P.) (K_2CO_3), a white granular powder of alkaline reaction, soluble in one part of water, very deliquescent. Dose, U. S. P., 1 gram; B. P., 0.12 to 0.3 gram.

POTASSII HYDROXIDUM (U. S. P., B. P.) (KOH), potassium hydrate, caustic potash—dry, white pencils or fused masses, deliquescent in the air and very caustic.

SODII BICARBONAS (U. S. P., B. P.) ($NaHCO_3$), a white opaque powder, with a cool, alkaline taste, soluble in eleven parts of water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

SODII CARBONAS (B. P.) ($Na_2CO_3.10\ H_2O$), colorless crystals with an alkaline reaction and taste, soluble in about two parts of water. Dose, 0.3 to 1 gram.

SODII CARBONAS EXSICCATUS (B. P.) (Na_2CO_3). Dose, 0.12 to 0.3 gram.

SODII CARBONAS MONOHYDRATUS (U. S. P.) ($Na_2CO_3.H_2O$), a white crystalline powder without odor and strongly alkaline. Dose, 0.25 gram.

LIQUOR SODII HYDROXIDI (B. P.), solution of sodium hydroxide.

TABELLÆ SODII BICARBONATIS COMPOSITÆ (B. P.), compound tablets of sodium bicarbonate, soda mint tablets. Dose, 2 to 6 tablets.

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2. **Acetates, Lactates, and Citrates.**—As far as their local effects are concerned, the acetates, lactates, and citrates of the fixed alkalies resemble the chlorides, owing any effect they possess to the salt-action.

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In the tissues, however, they are oxidized and form carbonates, so that the effects are those of the chloride before absorption, and those of the carbonate subsequently. The oxidation seems to proceed rapidly, and is very complete, over 95 per cent of the acetate, lactate, or citrate disappearing, and only some 2 to 3 per cent being excreted unchanged in the urine. The available alkali of the blood is increased as by the carbonates, and the urine is increased in amount and is less acid or may be alkaline.

The citrates are absorbed more slowly than the acetates or lactates and in sufficient quantity act as saline purgatives. The doses ordinarily prescribed, however, are too small to have this effect, and are also insufficient to induce any action after absorption except from that of the carbonate formed. Citrates form indissociable calcium salts and when they are injected intravenously they arrest the clotting of the blood and weaken the heart by throwing the calcium out of action. (See Calcium, Oxalate.) For this reason, sodium citrate cannot be used intravenously.

Therapeutic Uses.—Acetate and citrate of potassium have been largely used as diuretics and for increasing the alkalinity of the urine. They act here exactly as the alkaline carbonates and bicarbonates, but have the advantage of not neutralizing the gastric juice, or in any way affecting the digestion except from their salt-action, which may be minimized by exhibiting them in dilute solution. Sodium lactate is often administered intravenously in the form of a sixth molar solution in acidosis (as in diabetes) where it is desired to rapidly overcome an alkali deficiency. It is preferred to sodium bicarbonate for this purpose since it is more readily sterilized and will not cause necrosis if accidentally injected into the subcutaneous tissues.

Preparations

Potassii Acetas (U. S. P., B. P.) (CH_3COOK), a crystalline salt of pleasant, saline taste and very soluble in water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

Potassii Citras (U. S. P., B. P.) ($C_3H_4OH(COOK)_3$), a crystalline salt with a cool saline taste, readily soluble in water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

Potassii Citras Effervescens (U. S. P.), effervescent potassium citrate, a mixture of potassium citrate, sodium bicarbonate, tartaric acid and citric acid. Dose, 4 grams.

Sodii Citras (U. S. P., B. P.) ($Na_3C_6H_5O_7+2H_2O$), a crystalline salt with a cool saline taste, readily soluble in water. Dose, U. S. P., 1 gram; B. P., 1 to 4 grams.

Liquor Sodii Citratis Anticoagulans (B. P.), anticoagulant solution of sodium citrate.

Liquor Sodii Citratis cum Dextroso (B. P.), solution of sodium citrate with dextrose.

Tabellæ Sodii Citratis (B. P.), tablets of sodium citrate. Dose, 1 to 4 grams.

Sodii Lactas (B. P.), sodium lactate (70 per cent), CH_3:CHOH:COONa.

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3. **Ammonia and Carbonate of Ammonia.**—Ammonia solution and carbonate of ammonia differ considerably from the corresponding hydrates or carbonates of the fixed alkalies in their effects. Solutions of ammonia and of the carbonate give off ammonia freely, so that the effects are very similar, although the solution of ammonia is much the more powerful. Owing to its volatility, ammonia penetrates more rapidly and deeply than the fixed alkalies, and at the same time is less corrosive and less enduring in its effects. Applied to the skin in concentrated solution, it may corrode to some extent, but ordinary dilute preparations act merely as rubefacients, like the volatile oils. Even concentrated solutions do not dissolve the epidermis like the fixed alkaline hydroxides, but tend to penetrate through it and raise blisters. When inhaled, the irritation of the nasal mucous membrane causes a reflex stimulation of the vasomotor center, and consequent contraction of the arterioles and augmented blood-pressure, while the respiration is first arrested, and then becomes deeper and fuller. The heart may be temporarily slowed by inhibitory reflexes. Three parts of ammonia in 10,000 of air cause sneezing, pain in the nose, and tears, when inspired by man, and 5 parts in 10,000 are dangerous when inhaled for some time (Lehmann); the symptoms arise only from the local irritation and subsequent inflammation for any ammonia absorbed from the lungs is immediately neutralized.

Concentrated solutions cause corrosion of the mouth, esophagus and stomach similar to that seen in poisoning with the fixed alkalies, but some of the vapor, passing into the respiratory passages, often sets up spasm of the glottis, or such swelling of the mucous membrane of the larynx and trachea as to induce asphyxia. In cases of ammonia poisoning, therefore, the symptoms often arise, not so much from the gastric corrosion as from asphyxia, and death may occur very suddenly from this cause. The carbonate of ammonia, when swallowed, also causes slight gastric irritation, and in larger quantities nausea and vomiting.

After absorption, ammonia and its carbonates are rapidly changed to urea, and thus differ from the fixed alkalies in not increasing the available alkali of the blood, and in having no effect on the urine except to increase the urea and thereby cause some diuresis.

The carbonate of ammonia stimulates the central nervous system when it is injected into the blood in some quantity, but it has no such effect when absorbed from the stomach. (*Cf.* Ammonium Chloride, p. 58.)

Therapeutic Uses.—The aqueous solutions of ammonia are comparatively rarely employed. The liniment is used as a *rubefacient* in bruises and in other similar conditions. The gas arising from ammonium carbonate is often inhaled in cases of *fainting* or collapse, in order to elicit reflex stimulation of the medullary centers. The ordinary "smelling salts" used for this purpose consist of the carbonate reinforced with some of the strong solution and flavored with oil of lavender.

The aromatic spirits of ammonia and the carbonate (in solution) are used as mild *gastric stimulants* in debility, flatulence and alcoholism, and are very efficient for a short time. Large doses of the carbonate (2 grams) have been used as *emetics*, and do not cause such prolonged nausea as tartar emetic or ipecacuanha.

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The carbonate of ammonia and the spirits or even the ordinary water of ammonia are often given in cases of collapse or sudden *heart failure*. They are generally administered by the mouth and probably act here not directly on the heart and respiratory center, as has been supposed, but reflexly from gastric irritation. The action lasts only a very short time, but may be sufficient to tide the patient over an acute collapse. In depression from many different causes the aromatic spirits of ammonia is a favorite remedy, and probably owes its value to its gastric action, and not to any changes in the central nervous system. The carbonate is often added to other expectorant remedies to render the bronchial mucus excretion more fluid. This effect is mainly due to irritation of the stomach causing reflexly an increase in bronchial secretion. (See Ammonium Chloride, p. 58.)

Preparations

Ammonii Bicarbonas (B. P.), a white crystalline powder with a pungent taste and slightly ammoniacal odor. Dose, 0.3 to 0.6 gram in dilute solution.

Ammonii Carbonas (U. S. P., B. P.) is not the pure carbonate, but a mixture of somewhat varying composition, consisting of bicarbonate (NH_4HCO_3) and carbamate of ammonia ($NH_4NH_2CO_2$). It releases ammonia in the air and has therefore its pungent taste and smell. It forms translucent, crystalline masses, is very soluble in water and is contained in the aromatic spirit of ammonia. Dose, U. S. P., 0.3 gram (5 gr.); B. P., 0.3 to 0.6 gram.

Liquor Ammoniæ Aromaticus (B. P.), aromatic solution of ammonia. Dose, 1 to 4 mils.

Liquor Ammoniæ Dilutus (U. S. P., B. P.), diluted solution of ammonia, an aqueous solution of ammonia of 10 per cent strength by weight. Dose, B. P., 0.6 to 1.2 mils.

Liquor Ammonii Fortis (U. S. P., B. P.), strong solution of ammonia, a strongly caustic aqueous solution containing 28 per cent of NH_3.

Spiritus Ammoniæ Aromaticus (U. S. P., B. P.), aromatic spirits of ammonia, contains ammonia and ammonium carbonate along with several volatile oils dissolved in alcohol. Dose, U. S. P., 2 cc.; B. P., 1 to 4 mils. in a glass of water.

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See also Ammonium Chloride, page 58.

VI. ACIDS

Some acids owe their activity in the organism almost entirely to their acidity, *i. e.*, to the hydrogen ion, and may therefore be treated together. In the case of many other acids, such as prussic or salicylic acid, the effects of the acidity or hydrogen ion are insignificant in comparison with those of the rest of the molecule or the negative ion, and these are treated along with their salts.

Action.—The acids owe their action on living tissues to their neutralizing alkalies, to their withdrawing water when in concentrated form, and to their precipitating some of the proteins, more especially the globulins.

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Most living matter is neutral or slightly alkaline in reaction, and seems to be incapable of existing in acid media. Exceptions are met with in some of the moulds and in other vegetable organisms which live in somewhat acid solutions, but even these are destroyed by more concentrated solutions, perhaps because the acids precipitate their proteins. Acids are therefore **Protoplasm Poisons** and antiseptics of some power. Hydrochloric acid is found to delay the growth of organisms, and even to destroy the great majority of the less resistant forms in 0.2–0.3 per cent solution, or in the percentage in which it exists in the gastric juice. The others vary in strength largely according to their acidity. The inorganic acids are therefore more powerful as a general rule than the organic, which are less dissociated, and among the latter the simpler compounds are generally more active than those of larger molecule.

When sulfuric or nitric acid is applied to the **Skin** in concentrated form, it acts as a powerful caustic, destroying the epidermis and penetrating some distance into the skin and subcutaneous tissues, in which it causes necrosis. This is of course accompanied by great pain, and if much of the skin is attacked, by shock and collapse and symptoms similar to those seen in severe burns. Sulfuric acid causes a white, later a brown or black eschar, nitric acid a yellow. Hydrochloric acid is less liable to cause wholesale destruction of the skin, but penetrates the epidermis and raises blisters. The organic acids and phosphoric acid are still less irritant, but cause redness and even blistering when applied in concentrated solution. Dilute solutions of the acids may act as slight irritants to the skin, and often cause a feeling of stiffness and numbness, perhaps from precipitating the proteins.

The corrosive action of the acids is much more marked when they are applied to the less resistant **Mucous Membranes.** Even small quantities of strong sulfuric acid striking the eye are sufficient to destroy the sight.

In the **Mouth, Esophagus, and Stomach,** the corrosive action is evidenced by complete destruction of the mucous membranes which come in contact with the strong acid. The esophagus and stomach may be perforated, and this, along with the shock and collapse, often proves immediately fatal, or if the patient recovers temporarily, the erosions may give rise to cicatricial contractions. Hydrochloric acid and the stronger organic acids are capable of causing corrosion of the mucous membranes, but this is generally not so extensive as that following nitric and sulfuric acid. The corrosion produced by acids differs from that produced by alkalies in that the tissues become shrunken, hard and brittle, while after a caustic alkali they are soft and swollen, and have a slimy, soapy appearance.

The symptoms of corrosive acid poisoning are intense pain in the mouth, throat and stomach, vomiting, and often diarrhea, shock and collapse, with rapid, weak pulse and shallow respiration. The temperature is often subnormal and death occurs in the course of a few hours. When fuming acids are swallowed, and especially in poisoning with hydrochloric acid, the irritant vapor passing into the respiratory

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passages may cause spasm of the glottis, or edema of the larynx, and prove immediately fatal from asphyxia. Even one part of hydrochloric acid vapor in 20,000 of air causes sneezing and pain in the throat and chest.

Dilute solutions of the acids have a characteristic taste, and induce a reflex flow of saliva and an astringent feeling in the mouth and throat, from their causing a coagulation of the superficial layers of proteins. In the stomach they displace any weaker acids from their combinations with bases, and may have some antiseptic action, but do not influence the amount of secretion in any way. The gastric juice is normally acid, containing about 0.2 per cent of free hydrochloric acid, and this acid reaction is essential to the action of pepsin. Other acids may replace the hydrochloric acid in digestion, but both clinical experience and experiment point to hydrochloric acid as the most suitable acid for use in the stomach.

The acids are absorbed from the alimentary canal fairly rapidly in most cases. In the **Blood and Tissues** they do not exist as acids but as salts, for the reaction of the blood must remain slightly alkaline throughout life, and if sufficient acid be given to neutralize the alkalies of the body, the animal dies before the blood becomes neutral. Much larger amounts of dilute acids may be absorbed without serious symptoms by man and by the carnivora than by the herbivora. The explanation of this difference between the flesh-eating and the plant-eating animals is to be found in the nature of their food. The flesh-eaters are accustomed to the formation of some acid in their tissues, because the alkalies of their food are insufficient to neutralize the acids formed by the oxidation of the organic matter, and they would gradually be deprived of all their alkaline salts, therefore, were they not protected by the formation of ammonia. On the other hand, the herbivorous animals absorb much larger quantities of the organic salts of the alkalies in their food, and these, forming carbonates in the body, serve to neutralize what acid is formed in the tissues. In ordinary circumstances, therefore, they have no need to protect the fixed alkalies, and are unprovided with any mechanism for this purpose. When an excess of acid is absorbed, they neutralize it by means of the fixed alkali of the tissues and blood, and the slight change in the reaction reduces the power of the hemoglobin to transport carbonic acid from the tissues to the lungs. Thus in acid poisoning in rabbits, the alkali of the blood has been found to be so greatly reduced that the blood instead of containing some twenty-five volumes per cent of carbonic acid, carried only two volumes per cent or very little more than could be dissolved in the same amount of water. When this occurs, the tissues are unable to rid themselves of their carbonic acid, and a series of symptoms follow, commencing in deep, labored, rapid, afterward shallow, respiration; the heart is weak, a condition of collapse follows, and eventually the respiration ceases, the heart continuing to beat for some time longer. The injection of sodium carbonate, even in the last stage of intoxication, is followed by rapid recovery, from the restoration of the normal reaction of the blood and tissues.

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Acidosis.—When small quantities of acid are absorbed the acid is at once neutralized by the alkali bicarbonate of the blood, the resulting CO_2 stimulates the respiratory center and is got rid of by the increased ventilation of the lungs. A smaller amount of alkali remains in reserve in the blood, but this is remedied by the excretion of acid salts by the urine, so that the reserve quickly rises again. The only important symptom arising from a considerable reduction of the alkali reserve is breathlessness on exertion. If the alkali is further drawn upon by very large amounts of acid, death follows as has been described above.

The salts formed in the blood and tissues after the absorption of acids are rapidly **Excreted** by the kidneys, which, however, retain as much alkali as possible in the body and thus excrete the salts in an acid form. Hence there arises in some cases irritation of the kidneys, with albumin, and even blood, in the urine, which is rendered more acid than usual and causes a sensation of heat and smarting in the bladder and urethra. In the herbivora the reaction changes from alkaline to strongly acid, and large quantities of the salts of the alkalies appear, while in the carnivora some increase in the sodium and potassium of the urine occurs along with a much greater increase in the ammonia. The total nitrogen is somewhat increased from the large amount of ammonia, but the urea is slightly decreased, since it is from the latter that the kidney forms the ammonia with which the excess acid is excreted.

Therapeutic Uses.—The acids are used in medicine only to a limited extent, and most of the official preparations might well be dispensed with.

They may be employed to give flavor to draughts in fever and to quench the thirst, the most popular forms being those formed from fruits, such as lemons, limes, or grapes. The taste is due to the sugars, acids and volatile oils of the fruits, and is modified by the presence of inert colloid substances such as the pectins. The acids, of which citric, tartaric and malic are the chief, are very important factors in the effect, for if these be neutralized, the fruit juices become insipid, and do not quench thirst so thoroughly.

Acids are also used in certain forms of *dyspepsia*, and chronic diarrhea in which the hydrochloric acid of the stomach is deficient. Hydrochloric acid is most frequently prescribed for this purpose. Hydrochlorides of amino acids (*e. g.*, glutamic acid hydrochloride) which are solids, are also available. In *achylia gastrica*, which may be congenital, there may be a total absence of hydrochloric acid in the stomach. In *pernicious anemia* and malignant disease of the stomach, hydrochloric acid may be greatly reduced or absent. Grave lack of acid not only may prevent gastric digestion but also deprives the stomach of the antiseptic action of the acid. Also food tends to leave the stomach too soon because the reflex closure of the pylorus which is induced by high acidity of the duodenum fails to take place. The acid stimulus to secretin formation is also wanting. Improvement of digestion and of the general condition is often produced in these diseases by administration of dilute hydrochloric acid. However, many normal individuals have gastric achlor-

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hydria without manifesting any symptoms. In forms of dyspepsia arising from a sedentary life or in the course of convalescence, acid is often prescribed along with the bitter stomachics and is to be taken about one-half hour before meals. Irritation of the stomach or hyperacidity of the gastric juice, is, of course, a contraindication.

In achlorhydria, dilute hydrochloric acid, which is a 10 per cent solution, is administered in doses of 2 cc. well diluted with water. Although this amount of acid is insufficient to allow the appearance of free hydrochloric acid in the stomach, it will often relieve the symptoms of achlorhydria. The hydrochloride of glutamic acid may be used for the same purpose. Although the administration of hydrochloric acid renders the urine acid and thus less favorable to the growth of microbes, the acid forming salts such as ammonium chloride, calcium chloride or acid sodium phosphate are used for this purpose.

In cases of alkaline poisoning, the acids are the natural treatment; the organic acids should be preferred for this purpose, as they are less liable to cause additional corrosion, and acetic acid in the form of vinegar is more likely to be at hand than any other.

In every case in which acids are prescribed internally, they have to be given largely diluted, as otherwise they irritate the throat and stomach. They are taken through a glass tube, in order to prevent as far as possible their action on the teeth.

Externally, the acids are used to some extent as corrosives, strong nitric acid being used not infrequently to destroy small tumors, to cauterize the os uteri and for similar objects. Its action is more easily localized than that of potash and on the other hand is more powerful than the metallic salts, such as silver nitrate and zinc chloride. In dilute solution, they are sometimes applied to the skin to lessen excessive local sweating and diluted vinegar is often used to sponge fever patients.

In cases of corrosive **Poisoning** with acids, the first indication is to neutralize the acids as far as possible by giving alkalies. These ought not to be in themselves corrosive, and the best antidote is therefore the insoluble magnesia and magnesium carbonate. Lacking these, the most readily accessible alkali is the best, and the lime may be scraped from the walls or ceilings, or chalk, soap, or wood ashes may be given. The walls of the stomach and esophagus may also be protected by giving milk or white of egg, or the acid may be rendered less corrosive by diluting it with large quantities of water.

Sulfuric Acid is one of the most corrosive acids when it is applied in concentrated form, and often induces complete charring of the tissues, and a coal-black slough.

Acidum Sulphuricum (U. S. P., B. P.), 95 per cent.

Acidum Sulphuricum Dilutum (U. S. P., B. P.) contains 10 per cent of absolute sulfuric acid. Dose, B. P., 0.3 to 4 mils.

The sulfuric acid preparations are not largely used.

Nitric Acid is equal or superior to sulfuric in its corrosive action. It stains the skin and tissues a bright yellow or yellowish-brown, and this serves to distinguish cases of poisoning under the two acids.

Acidum Nitricum (U. S. P., B. P.) contains 70 per cent of absolute nitric acid (HNO_3).

A glass rod dipped in concentrated nitric acid is used as a corrosive.

Hydrochloric Acid is less corrosive than the two preceding acids, and tends to cause blistering on the skin rather than necrosis. It may cause actual loss

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of substance, however, when applied to the mucous membranes in concentrated form, and stains the mouth a whitish color.

Acidum Hydrochloricum (U. S. P., 36 per cent, B. P., 32 per cent).

Acidum Hydrochloricum Dilutum (U. S. P., B. P.), contains 10 per cent of hydrochloric acid gas. Dose, U. S. P., 4 cc.; B. P., 0.3 to 4 mils.

Phosphoric Acid is much less corrosive and irritant than the other mineral acids, but in large, concentrated doses may cause gastro-enteritis.

Acidum Phosphoricum (U. S. P., B. P.) contains 88 per cent of H_3PO_4.

Acidum Phosphoricum Dilutum (U. S. P., B. P.), a 10 per cent solution. Dose, B. P., 0.3 to 4 mils.

The acidity of the urine arises from the excretion of acid phosphates for the most part, and may be increased by the administration of *Sodii Biphosphas* (U. S. P.); *Sodii Phosphas Acidus* (B. P.), NaH_2PO_4. This consists of colorless crystals with an acid saline taste, readily soluble in water. Dose, U. S. P., 0.6 gram; B. P., 2 to 4 grams.

The **Organic Acids** have a much less marked local action than the inorganic, causing little or no corrosion unless when applied to mucous surfaces in very concentrated form. They are absorbed as salts of the alkalies, but do not as a general rule reduce the available alkali of the blood or render the urine more acid, because they are oxidized to carbonates in the tissues. Those which are not burned in the tissues, such as oxalic acid and the aromatic acids, have the same effects as the inorganic acids on the alkali reserve and the urine.

Acetic Acid applied in concentrated solution to the skin causes irritation and congestion and eventually blistering, but does not induce necrosis except of the most superficial layers. The congestion is often followed by marked pallor instead of by blistering; and this has been explained by contraction of the vessels, but may be due to a precipitation of the proteins of the skin. In the mouth and stomach it acts as an irritant, causing vomiting, great pain, collapse and even death; the epithelium is found thickened and occasionally contains hemorrhages. Dilute acetic acid (vinegar) has little effect apart from its acid taste, and is used largely as a flavoring agent and condiment. The prolonged use of large quantities may, however, give rise to gastric irritation and to loss of appetite and weight.

Acidum Aceticum Glaciale (U. S. P., B. P.) contains 99 per cent of acetic acid.

Acidum Aceticum (U. S. P., B. P.) contains 36 per cent of absolute acetic acid U. S. P., 33 per cent B. P.

Acidum Aceticum Dilutum (B. P.) contains 6 per cent of absolute acetic acid. Dose, 2 to 4 mils.

Acetic acid is sometimes applied to the skin as a slight local irritant in contusions, and in very dilute solutions to cool the surface and to prevent excessive local perspiration. It has been used as a styptic in slight hemorrhage, and may be inhaled for this purpose in epistaxis. Vinegar is also inhaled in cases of fainting, in order to induce reflex stimulation of the vasomotor center through irritation of the nostrils. In cases of poisoning with alkalies vinegar is often the most convenient acid, and in addition is less likely to do harm than the inorganic acids. Glacial acetic acid is a powerful caustic.

Acetic acid itself is not used as a corrosive, but one of its derivatives, trichloracetic acid (CCl_3COOH), U. S. P. and B. P., has been employed with good results.

Formic Acid resembles acetic acid in most points, except that it is more volatile and more irritant, that less of it is oxidized in the tissues, and that given in large quantities it is said to induce nephritis. It is quite useless in therapeutics.

The other acids of the acetic acid series resemble it in their effects, but become less irritant as they become more complex and less easily dissociated.

Lactic Acid resembles acetic acid in its behavior in the organism.

Acidum Lacticum (U. S. P., B. P.), containing 87 per cent of lactic acid, has been used as a caustic application to malignant ulcers and diphtheritic membranes.

Oxalic Acid is frequently used as a poison by suicides, either as such or the acid potassium salt (salt of sorrel or essential salt of lemons). Poisoning has

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repeatedly occurred from oxalic acid having been mistaken for magnesium sulfate, which it resembles in appearance. The symptoms are those of acid poisoning, along with the specific effects of the oxalates. Oxalic acid is not used in therapeutics.

Tartaric Acid induces symptoms of gastric irritation when taken in large doses, and has been the cause of fatal poisoning in a few cases. It is slowly absorbed, and some of it escapes combustion in the tissues and is excreted in the urine in the form of acid tartrate. (See Tartrates, page 242.)

Acidum Tartaricum (U. S. P., B. P.) ($H_2C_4H_4O_6$), colorless crystals, very soluble in water. Dose, B. P., 0.3 to 2 grams.

Tartaric acid is prescribed with the carbonates and bicarbonates to form effervescent draughts; the tartaric acid ought to be slightly in excess in order to lend its pleasant acid taste, the usual proportion being about eight parts of acid to seven parts of sodium bicarbonate. These effervescent mixtures formed with the tartrates act as saline cathartics in large doses (see page 242). Tartaric acid may be prescribed in dilute solution with sugar and a drop of volatile oil as a lemonade, which is cheaper than that formed with citric acid.

Citric Acid resembles tartaric acid in its action, but appears less irritant, and no case of serious poisoning is recorded from its use. It is slowly absorbed like tartaric, but seems to be almost entirely oxidized in the tissues.

Acidum Citricum (U. S. P., B. P.) ($H_3C_6H_5O_7+H_2O$) resembles tartaric acid in its properties for the most part. Dose, B. P., 0.3 to 2 grams.

Syrupus Acidi Citrici (U. S. P.) is ordinary syrup to which 1 per cent of citric acid and tincture of lemon-peel have been added, and is used only as a flavor.

Citric acid and the citrates when added to drawn blood prevent clotting by combining with the calcium in a practically non-dissociating salt. When administered by the mouth it has no such effect on the circulating blood, and its use to lessen clot formation in the body is based on erroneous observation.

Citric acid is used to form lemonades and effervescent draughts. For lemonade two to four parts of citric acid may be dissolved in 1,000 parts of water, some sugar and a few drops of volatile oil being added. For effervescent solutions about eight parts of the acid may be prescribed along with seven parts of bicarbonate of soda, with directions to dissolve the two powders separately, mix the solutions and drink while effervescing. In large quantities this mixture acts as a saline cathartic; in smaller quantities it may be used to increase the alkali of the blood, and to render the urine less acid.

Lime juice and lemon juice, which contain considerable amounts of free citric acid, are generally preferred to the pure acid for lemonades to quench the thirst. Lime juice has been found of great benefit as a prophylactic in the treatment of scurvy, but this is not due to the citric acid, but to the vitamin of the fruit juices (page 602).

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VII. OXYGEN

Ever since the discovery of the relation of oxygen to the respiration, attempts have been made to use it in therapeutics especially in cases where the blood seems to be insufficiently oxygenated. Air contains 20.93 per cent of oxygen, and normally the alveolar air contains about 14 per cent of oxygen, which, at ordinary barometric pressures, is equiva-

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lent to an oxygen pressure of approximately 105 mm. of mercury. At this pressure the amount of oxygen in simple solution in the blood is 0.3 volume per cent, while the amount of oxygen in combination with hemoglobin will be 18.5 per cent. As the hemoglobin is under these conditions already 95 per cent saturated with oxygen, increase in the percentage of oxygen in the alveolar air cannot materially alter this; but the amount of oxygen in solution can be increased from 0.3 to a maximum of 2.2 volumes per cent when pure oxygen is respired. Under normal conditions, therefore, an increase of only about 15 per cent in the oxygen-carrying capacity of the blood can be attained even by the inspiration of pure oxygen. At first sight this would seem to be discouraging to the use of oxygen as a therapeutic measure, but in abnormal conditions of oxygen want in which the oxygen content of the arterial blood is reduced, an increase in the oxygen content of the alveolar air may be of great advantage. Moreover, where the breathing is labored, the use of oxygen will reduce the respiratory efforts necessary for aerating the lungs and thus prove of benefit to the patient.

The normal functioning of all the tissues in the body is dependent upon their receiving a sufficient supply of oxygen. This supply may be inadequate owing either to the blood receiving or absorbing insufficient oxygen or to the circulation in the tissues being defective. Conditions of oxygen lack may be conveniently arranged under the following groups.

1. *Anoxic Conditions.*—In these, owing to alteration in the atmospheric environment or to impairment of the gaseous exchanges in the lungs, the arterial blood does not contain its normal amount of oxygen. This may occur, for example, where there is an insufficient partial pressure of oxygen in the inspired air, as in mountain sickness. It may occur when for any reason there is an impediment to the normal entry of air into the lungs, *e. g.*, in laryngeal or bronchial obstruction, or when an area of the lung is partially or totally unventilated. One of the most important pathological conditions which may produce this condition is an inflammatory or edematous thickening of the alveolar epithelium, which may necessitate an increased partial pressure of oxygen in the alveolar air in order that normal amounts of oxygen may reach the blood. This condition may be present, for example, in pneumonia or pulmonary edema.

2. *Anemic Conditions.*—The supply of oxygen to the blood may be normal, but the oxygen-carrying capacity of the blood may be deficient. This will happen when there is a deficiency in the actual quantity of hemoglobin (*e. g.*, in certain anemias) or in the available hemoglobin (*e. g.*, in carbon monoxide poisoning).

3. *Circulatory Conditions.*—In some conditions of circulatory failure, though the amount of oxygen in the arterial blood may be within normal limits, the blood passes so slowly through the capillaries that the blood becomes unduly desaturated as regards oxygen. The anoxemia of circulatory failure is primarily a stagnation anoxemia.

4. *Tissue Conditions.*—In certain types of poisoning, notably with cyanides, the tissues are relatively incapable of taking up oxygen even if it is supplied to them in normal amounts by the blood.

It will be evident that the administration of oxygen will be of greatest

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value in conditions of anoxic anoxemia, and of little usefulness in anoxemia due to circulatory failure since in this condition the blood leaving the lungs is adequately aerated. Nor will oxygen be of value in conditions where the tissues are unable to use oxygen. In anemic conditions oxygen will be of value in carbon monoxide poisoning where its administration (with carbon dioxide to stimulate the respiration) aids in displacing the carbon monoxide from its combination with hemoglobin.

The symptoms of oxygen lack vary greatly according to the degree of oxygen lack and the rapidity with which it is induced, but among the important symptoms are hyperpnea, cyanosis, increased pulse rate, fall of blood-pressure, and progressive depression of the central nervous system. It is important to remember that cyanosis does not commence to be apparent until the oxygen saturation of the arterial blood has fallen to 80 or 85 per cent, and that even before this stage is reached, damage may be done to the myocardium or central nervous system. Oxygen ought therefore to be given, if possible, before cyanosis develops, and to be given in larger quantities than will merely remove the cyanosis if that is present. The ideal would be to administer just sufficient oxygen to restore the oxygen saturation to the normal level. Blood-gas estimations are necessary to determine this accurately, but these are not always practicable, and the value of oxygen administration must usually be judged by the relief of symptoms of oxygen lack.

Therapeutic Uses.—Oxygen therapy is of greatest value in pneumonia where the consolidation, effusion of fluid and edema of the pulmonary tissue interferes with the absorption of oxygen from the alveoli. This is evidenced by the cyanosis and decreased oxygen content of the arterial blood. Administration of oxygen abolishes the cyanosis and dyspnea, reduces the pulse rate and improves the subjective condition of the patient.

Oxygen is also of value in pulmonary edema and in severe exacerbations of bronchitis, asthma, emphysema and bronchiectasis. In cardiac decompensation where there is cyanosis, in acute coronary occlusion, and in attacks of paroxysmal dyspnea, the administration of oxygen is of value.

The use of oxygen (with carbon dioxide) in carbon monoxide poisoning has already been mentioned. Oxygen is also used in anesthesia in conjunction with certain anesthetics (nitrous oxide). It has been advocated for use in abdominal distention, to relieve the symptoms following pneumoencephalography, in head injuries and in numerous other conditions where it is desirable to increase the oxygen content of the blood or tissues.

Though any good effect derived from oxygen therapy is, as a rule, evanescent, it is important to realize that often a permanent effect may be obtained from its breaking a vicious circle. Usually, it should be given as continuously as possible and the benefit to be obtained from it depends largely upon the efficiency of the method of its administration.

Methods of Administration.—Oxygen is stored in steel cylinders at high pressure. It is difficult to devise a method of administering it

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which will provide an adequate raising of the oxygen in the alveolar air, without an expensive wastage of oxygen and without employing an apparatus which will be cumbrous, expensive and in practice disagreeable to the patient.

Administration of oxygen by a *nasal catheter* is frequently employed. This method was first used in France on "gassed" men, and had the advantage that several cases could be treated at once from the same cylinder. One disadvantage is that the rate of oxygen flow necessary to produce a satisfactory increase in the alveolar oxygen percentage is so large that great discomfort is caused, except in subjects where the respiratory minute volume is small and the necessary rate of oxygen flow is therefore less, as, for example, in children. In the latter it has been found (Bourne) to give excellent results if the anoxemia is treated early, before the arterial oxygen saturation has had time to fall greatly. As an emergency method it has the advantage of simplicity and moderate efficiency when used for adults.

In the above described method the oxygen passing during the expiratory phase is wasted, and only exceptionally is it possible to raise the oxygen percentage in the alveolar air to the optimum point. To obviate these drawbacks, a more complicated apparatus is necessary such as the use of a mask and valves for conserving the oxygen during expiration and raising the available percentage of oxygen. While more efficient than the nasal catheter, this method has the serious drawback that many patients cannot tolerate the mask.

Oxygen chambers are in use in hospitals and may be rented for use in the home. The patient is placed in a specially constructed chamber or in some type of bed-tent, where the oxygen percentage can be raised to any desired degree. Because of the inflammatory nature of objects when placed in oxygen, it is imperative that no open flame be brought into the room where an oxygen tent is in use.

The use of carbon dioxide combined with oxygen is referred to later.

Toxicity.—It has long been known that small animals (rats, mice), plants, fishes and certain lower organisms succumb when subjected to pure oxygen for some time. In the mammal death results with congestion and edema of the lungs and a fibrinous bronchopneumonia. The high percentage of oxygen apparently is an irritant of the pulmonary epithelium. In man, however, there is no evidence that a similar irritant effect is induced when the subject is subjected to 90 to 100 per cent oxygen for a period of one or two days. Nevertheless prolonged administration except in rare cases is undesirable in order to avoid any possible deleterious action similar to that seen in the lower mammals.

Ozone (O_3), is a much more powerful oxidizing body than ordinary oxygen, but is more easily reduced than peroxide of hydrogen. It has a curious phosphorous odor and is distinctly irritant to the respiratory membranes; it is almost always accompanied by nitrogen oxides, and these may further aggravate this local irritation. It is rapidly decomposed by living matter, and is certainly not absorbed into the blood unchanged; in fact it is immediately destroyed on the pulmonary surfaces. In man its inhalation in a dilution of 2 to 3 per million of air causes drowsiness and headache from irritation of the frontal sinus. In animals 15 to 20 parts of ozone per million of air sometimes proves fatal

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in a few hours from respiratory irritation; a condition of weakness and drowsiness precedes death, apparently as a result of the local irritation, and the lessened movement is accompanied by a fall in the CO_2 eliminated. Ozone injures most enzymes and the fermentation of yeast is hindered, but the lactic fermentation does not seem to be affected and some others are merely delayed. Ozone applied to the seeds or leaves of the higher plants also delays their development and injures them.

Ozone has undoubtedly disinfectant properties, but these are only apparent when air contains 15 mg. or more per liter. Even this disinfects only the air itself and the surfaces of objects, as the ozone loses its oxidizing properties whenever it comes in contact with organic matter and therefore fails to penetrate. It has been advocated to disinfect drinking water, but is efficient only in fairly pure waters, as any organic matter is oxidized and thus absorbs the ozone and the microbes escape. For this reason it cannot be used to sterilize milk or food.

Preparations

Oxygenium (U. S. P., B. P.) contains not less than 99 per cent (U. S. P.; B. P., 98 per cent) by volume of oxygen gas. It is supplied compressed in metal cylinders. Because of the greater inflammability of burning objects in an atmosphere of oxygen, great caution must be used against open flames in the vicinity of oxygen tents.

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VIII. CARBON DIOXIDE

Carbonic acid is contained in considerable quantity in many therapeutic preparations, notably in the effervescent cathartics and antacids, and also in many beverages, such as soda water, potash water, champagne and other sparkling wines. In some of these it is formed by the action of an acid such as citric or tartaric acid on carbonates, in others it is liberated in the course of fermentation, while in the artificial aerated waters it is forced into solution under high pressure. The last are therefore simple solutions of carbonic acid, while in the others more powerful agencies—cathartic salts or alcohol—are contained in addition.

Carbonic acid has a weak irritating action when applied in quantity; thus in baths charged with carbonic acid, a slight reddening of the skin has been observed, and some irritation and prickling of denuded surfaces is produced; a stream of carbonic acid directed against a wound or burn causes considerable heat and pain. Pure carbonic acid gas causes spasm of the glottis when inhaled, and even when it is much diluted, some irritation in the respiratory passages may follow at first. Solutions of carbonic acid induce reddening of the mucous membrane of the mouth and stomach, and are very rapidly absorbed, owing to the congestion and increased blood flow in the stomach wall which follows their administration. Much of the carbonic acid is

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thrown up by eructation, but some of it is absorbed and is excreted by the lungs. The absorbed acid has no effect on the organism, but the slight irritation of the stomach may cause increased appetite and a feeling of well-being. The rapid absorption of the water in which it is dissolved is followed by an augmented secretion of urine, and the carbonic acid waters are therefore used in preference to ordinary waters where a rapid flushing of the tissues and a profuse secretion of urine is desired. In addition, the slight irritation of the mouth and stomach renders them more acceptable than ordinary waters in fever and in other diseases accompanied by intense thirst; a mixture of milk and aerated water is often very grateful. The presence of carbonic acid in the sparkling wines leads to the rapid absorption of the alcohol also, and this action on the stomach may explain their being more exhilarating than other wines containing an equal amount of alcohol. The slight irritant effect of carbonic acid in the stomach has proved of benefit in some forms of gastric catarrh, such as that following alcoholic excess. Carbonic acid waters are also useful in the vomiting of pregnancy and in seasickness.

The prolonged application of carbonic acid to the mucous membranes leads to local anesthesia, and numbing of the skin is also stated to occur under similar treatment.

Carbon dioxide is absorbed from all the mucous membranes, from the skin and from the lungs. The gas has no effect after absorption except when inhaled, however, as when absorbed in any other way it is at once excreted by the lungs, and the amount absorbed never alters appreciably the normal percentage of carbonic acid in the blood.

Toxicity.—When carbon dioxide is inhaled unmixed with oxygen, it induces asphyxia, partly from a specific action which it exerts on the central nervous system, but chiefly from the absence of oxygen. Its effects are, therefore, very similar to those of any indifferent gas, such as hydrogen or nitrogen, and the symptoms are those of ordinary asphyxia. When, however, CO_2 is inhaled mixed with a sufficient amount of oxygen, the specific effects of the gas are observed without any asphyxia. The symptoms are those of transient stimulation and subsequent depression of the central nervous system and heart. The first stage is marked by a very short period of psychical exaltation, with deep respirations, a slight rise in the blood-pressure and a moderately slow pulse. Very soon, however, unconsciousness, loss of the spontaneous movements, and later of the spinal reflexes follow, the respiration becomes somewhat slower and shallower, the pulse continues slow and the heart is weaker. If the inhalation be continued the respiration fails, the heart continuing to beat for a short time, though weakly. The symptoms of the first stage seem to be due to a direct stimulant action on the cerebrum and on the vagus, vasomotor, and respiratory centers, while the second stage resembles that induced by the ordinary anesthetics, and is evidently caused by depression of the central nervous system and of the heart muscle. In fact a mixture of CO_2 and air has been used as an anesthetic in one or two surgical operations. Death from carbonic acid poisoning is not preceded by convulsions, those observed in ordinary asphyxia being due to the absence of oxygen, and not to the excess of carbonic acid; it is still undecided by which of these factors the increased peristalsis seen in suffocation is caused. In well diluted vapor the symptoms of exaltation alone are observed, no anesthesia following. A mixture of 5 per cent CO_2 in air causes acceleration and deepening of the respiration without further changes.

Carbonic acid in excess acts as a poison to other organs besides the central nervous system and the heart, although this effect is not seen in mammals.

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Frog's muscle loses its irritability rapidly, the ciliated epithelium ceases movement and the motor nerves, after a short period of increased excitability, are paralyzed by exposure to an atmosphere of carbonic acid. The blood assumes the venous color when shaken with the gas, and prolonged contact produces acid hematin, as does any other acid. It is a general poison to the protoplasm in mammals, apart from the effects on the central nervous system, for the combustion in the tissues is lessened to an extraordinary degree, as is evidenced by the very small amount of oxygen absorbed.

Therapeutic Uses.—Carbon dioxide is the natural and the most effective stimulant to the respiratory center. Pure air contains about 0.04 per cent of CO_2, while a badly ventilated room may contain several times that concentration. The addition of CO_2, up to a certain point, to the inspired air causes an increase in the lung ventilation. For example, the addition of 2 per cent of CO_2 may increase the volume of air breathed by about 50 per cent, 5 per cent CO_2 by as much as 500 per cent, the increase

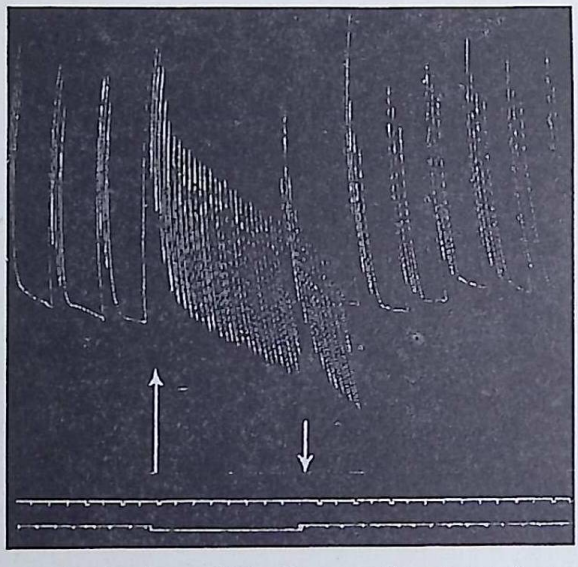

FIG. 4.—Periodic respiration in a rabbit. Between the arrows, 6 per cent CO_2 in air was inhaled and the respiration became regular, but relapsed again soon afterward.

in the former case being due to greater depth of respiration, in the latter case also to increased frequency. With higher percentages toxic effects may appear.

The stimulating effect of CO_2 inhalations will occur to the degree mentioned above only when the respiratory center is normally excitable. When the respiratory center is depressed, *e. g.*, by narcotics or prolonged defective blood supply, the effects will be less dramatic.

The inhalation of oxygen containing 5 to 7 per cent of CO_2 has been used in a variety of conditions to stimulate the respiratory center and to prevent collapse of the lungs, especially in asphyxia due to drowning or in asphyxia of the newborn, and in poisoning by carbon monoxide, morphine, etc. In some forms of Cheyne-Stokes respiration it has been found that carbon dioxide restores regular breathing (Fig. 4). Inhalations of CO_2 have been strongly recommended for the prevention of lung complications following the use of anesthetics, especially ether.

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During unconsciousness produced by ether or arising from any other cause, the stoppage of voluntary movement, the cessation of changes of posture and especially the suppression of coughing tend to prevent the natural removal of mucus from the bronchi. This accumulation of mucus may block the smaller bronchi, leading to collapse of areas of the lung, and so favor bacterial infection. The increased respiratory movements produced by CO_2 tend to prevent this collapse of the lung. It also accelerates the excretion of the anesthetic by the lungs. For these reasons, short periods of inhalation of CO_2 administered during recovery from anesthesia are believed to be of value in preventing lung complications. When respirations are arrested, inhalation of CO_2 must of course be effected by some form of artificial respiration.

Preparations

Carbonei Dioxidum (U. S. P., B. P.) contains not less than 99 per cent of CO_2 and for convenience is usually compressed in metal cylinders.

Mixtures of oxygen and carbon dioxide compressed in steel cylinders are also available commercially.

Solid carbon dioxide (dry ice) is occasionally used for the local application of cold and for its escharotic effects.

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IX. CARBON MONOXIDE

Carbon Monoxide (CO) which results from the incomplete oxidation of compounds containing carbon, is of toxicological interest since it often gives rise to fatal poisoning. The exhaust gas of automobiles and illuminating gas used in the household are the commonest source of carbon monoxide poisoning. Carbon monoxide forms a stable compound with hemoglobin, carboxyhemoglobin, which prevents this blood pigment from transporting oxygen to the tissue and hence asphyxia ensues. The concentration of carbon monoxide in the inspired air and the time during which it is inhaled will determine the amount of the noxious gas absorbed and hence its harmfulness. As expressed by Henderson and Haggard, if the product of the hours of exposure by the parts of carbon monoxide present in 10,000 parts of air, exceeds nine, symptoms are elicited which at fifteen become dangerous to life. Thus air containing 0.1 per cent (ten parts per 10,000) is dangerous if inhaled for one and one-half hours or longer.

The **symptoms** of carbon monoxide poisoning are those of anoxia with headache, weakness, dizziness, tachypnea, nausea, etc., leading ultimately to coma, respiratory failure and death. The skin and mucous membranes assume a cherry red appearance due to the bright red color of carbon monoxide hemoglobin.

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Treatment of carbon monoxide poisoning consists in removing the carbon monoxide from the blood. This is best done by the administration of oxygen containing 5 to 10 per cent of carbon dioxide. Permanent damage to the central nervous system, particularly of the higher centers, may result and as a consequence a fatal outcome may still ensue following the elimination of the gas and apparent improvement.

Numerous other toxic gases such as hydrocyanic acid, benzol, etc., are discussed elsewhere. Of recent years the introduction of many new organic gases as mechanical refrigerants, as insecticides, etc., has given rise to numerous instances of poisoning by these compounds. Methyl bromide used as a fumigant, fire extinguisher and refrigerant is an example of such compounds which have given rise to poisoning.

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X. HELIUM

Helium is one of the inert rare gases which is occasionally used in medicine because of its lightness. A mixture of 80 per cent helium and 20 per cent oxygen is only one-third as heavy as air and hence this mixture is breathed with much less effort than air. It is therefore used where there is respiratory obstruction and dyspnea as in status asthmaticus. Because of its ready diffusibility and low solubility compared to nitrogen it is also useful in decompressing divers subjected to high pressure. The incidence of "divers' bends," caused by the release of nitrogen in the body, may be appreciably reduced by using a mixture of helium and oxygen rather than air in the pressure chamber or during the decompression period.

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XI. THE HEAVY METALS AND METALLOIDS

A. HEAVY METALS

A large number of important drugs belonging to the chemical series of heavy metals resemble each other so closely in their action in living organisms that they may be readily grouped together in a division of the pharmacological system. There is both chemical and pharmacological justification for separating the group of the heavy metals proper from their near relatives the metalloids, though the transition from the former, through bismuth and antimony, to arsenic and phosphorus, is a gradual one. Bismuth might almost equally well be grouped with the heavy metals and even antimony is sometimes included in that group; but there are at least reasons of convenience for the subdivision here adopted.

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The metals as such do not induce any symptoms except from their mechanical properties. Thus mercury may be swallowed in large quantities without causing mercurial poisoning, and silver or copper coins are equally devoid of effect as poisons. They are active only when they are capable of dissociation into ions of the metal or of an oxide. Thus potassium ferrocyanide does not cause any symptoms of iron poisoning when it is injected into a vein, because the iron passes through the body undissociated, and any effects are due to the ferrocyanide ion and not to the iron. In the same way compounds of the metals with ethyl and methyl, such as lead triethyl, have an action quite different from that of lead, as long as they remain undecomposed in the tissues, but eventually induce metallic poisoning, as they are broken up into bodies from which the lead or lead oxide ion can be dissociated.

The action of the heavy metals consists of two parts, the local effects induced at the point of application, and the general effects which follow the absorption of the poison into the blood and tissues. Either of these may be produced alone by suitable preparations and modes of administration, and they are to be regarded as entirely independent of each other.

The Local Action of the heavy metal series is due to their precipitating proteins in very dilute solutions. Proteins are also thrown out of solution by salts of the alkalies and alkaline earths, but only when these are present in much higher concentration than is necessary in the case of the heavy metals; and the precipitate formed by the salts of the alkalies is reversible, that is, it can be redissolved by the addition of water.

When a salt of a heavy metal is added to a solution of egg albumin, or similar protein, a precipitate is formed consisting of proteins and a variable amount of the metal or its oxide, while free acid remains in solution. The precipitate is insoluble in water but is dissolved by neutral salts, including those of the heavy metals, so that the addition of more metallic salt may redissolve it; similarly the addition of more protein solution may redissolve it by increasing the supply of neutral salts. The precipitate contains the metal in an insoluble form, and the latter may be detected by the ordinary reactions; thus the protein precipitate from iron salts is blackened by ammonium sulfide in the same way as ordinary iron.

On subjecting these precipitates to certain chemical manipulations, however, the metal seems to become more firmly attached to the protein, for ammonium sulfide acts on it much more slowly. The metal is then said to be masked, because its presence is not so readily detected as in ordinary combinations. Partially masked preparations have been formed artificially, but in the body the process is carried much further, for in many of their protein compounds the metals cannot be detected by any of the ordinary tests, however long the reagents may remain in contact with them, and their presence is recognized only when the protein is destroyed by heat or other similar agencies.

When a solution of a metallic salt comes in contact with a living tissue, such as the mucous membrane of the mouth or stomach, the

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same precipitation of protein and metal occurs and the acid is liberated; the local action appears to be determined by the combined effects of these factors. The more completely dissociated the ions of the salt are, the more rapid is the reaction with protein, and the more intense the local action. Thus the more readily ionized inorganic salts act more strongly than the organic ones, which are slowly dissociated, and these in turn are more liable to cause marked local changes than the double salts, which are dissociated with difficulty. The activity of the acid liberated also varies with the extent to which it is dissociated into ions; it therefore exercises the same astringent or corrosive effects as if it had been applied uncombined, but its action may be modified by the presence of a layer of precipitate protecting the surface. Thus when a weak solution of lead acetate is applied to a mucous membrane, a precipitate is formed in the proteins lying on the surface, and protects the cells from the action of the very dilute acetic acid which is set at liberty. If a stronger solution be applied, however, the metallic precipitate extends into the cell, while the acetic acid, being more concentrated, exercises some irritant action. As the concentration increases, the deeper parts of the epithelial cells are coagulated, and at the same time the acid becomes more destructive, so that eventually the superficial layer of the epithelium is killed and the deeper layers are attacked. The acetate of lead may thus act as an astringent, covering a mucous surface with a protective pellicle of insoluble precipitate, or as an irritant, which induces an increase in the circulation of the part, a more rapid division of the cells and an effusion of liquid, or as a corrosive, involving the superficial layer of cells, and sometimes even the deeper ones, in its destructive effects.

When the nitrate of lead is applied, the astringent effect is much less evident, the irritant and corrosive more marked, because the salt is more readily dissociated and the reaction is therefore more rapid, and, in addition, the nitric acid is much more corrosive than acetic acid. The same metal attached to different acids may therefore induce very different effects, in the one case acting chiefly as an astringent, in the other as an irritant and corrosive.

The character of the metal which is carried down in the precipitate also influences the local effect; thus mercury is intensely poisonous and destroys the cells in which it is deposited, while lead is a less powerful poison and the cells may recover even if lead has been deposited on them. In addition, salts which have a very strong affinity for water withdraw fluid from the cells, and thus act more strongly on them than others which have not this character; for example, dried alum is much more destructive to the tissues with which it comes in contact than alum containing its ordinary water of crystallization.

The different metallic salts therefore vary in their local action within wide limits—from the formation of mildly astringent membranes to the production of widespread necrosis and destruction of tissue.

The most powerful corrosive salts of any metal are those which are most rapidly dissociated into ions, that is, the chlorides and nitrates, provided they are soluble. The sulfates are much less irritant, because

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they are less readily dissociated, and perhaps because the sulfuric acid may fail to penetrate the cells, owing to its being less volatile and its anion having less permeating power than that of hydrochloric or nitric acid. The iodides and bromides are generally regarded as less irritant than the chlorides, but are less frequently used and less well known.

The least corrosive of the salts of the metals are those formed with the slowly dissociated organic acids, such as the acetates, tartrates or citrates. When these are united with a metal which in itself is not a very active poison, such as lead, they are almost purely astringent. On the other hand, the acetate of silver or of mercury tends to be irritant and corrosive, from the poisonous action of these metals on the tissues. In any case, the acetates are less irritant than the corresponding chlorides and nitrates, provided they are equally soluble.

The local action also varies in the same salt of different metals. Lead is the most astringent of the metals ordinarily used in solution, while mercury salts have little or no astringent action, owing to their specific poisonous action on the cells. Iron and aluminum approach most nearly to lead, then copper, zinc and silver, and at a longer interval, mercury.

It is impossible to arrange the metallic salts as either astringents or irritants, because in every instance the effect varies with the concentration, and with many other features, such as the condition of the surface to which they are applied, and the quantity of protein with which they come in contact before they reach the living membrane.

The insoluble salts come into less intimate contact with the tissues, and have much less effect; but many of them are slowly taken up and may then act as irritants or astringents. The insoluble preparations of mercury tend to irritate and corrode the surfaces to which they are applied, but the insoluble salts of the other metals are generally astringent. It is difficult to determine how far the so-called astringent and protective action of these insoluble substances is due to the formation of precipitates, and how far to their acting mechanically as protective coverings over irritated surfaces, but the latter factor is undoubtedly the more important in many instances.

If the metal is applied in the form of an "albuminate," that is, in the protein precipitate, the effects are the same as if it were used in any other insoluble form; for example, the "albuminate" of lead and most metals cause no irritation, but that of mercury acts as an irritant.

The precipitation induced by the astringents involves only the surface layer of cells, but the membrane formed protects the part from mechanical and chemical irritation, and thus lessens congestion and inflammation. It also renders the surface less permeable and so may check exudation. Some authors maintain that the astringents contract the vessels by direct action on their coats, or lessen secretion by direct action on the secretory cells, but these statements are not satisfactorily established, and the changes may be the indirect results of the protection afforded to the surface cells. When irritation is induced, the vessels of course dilate, and congestion and exudation follow.

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Many of the metallic salts are powerful disinfectants, partly no doubt from their coagulating the proteins of the microbes, but also from a specific poisonous action on them, which is quite distinct from their precipitating action. As a general rule the disinfectant power varies with the degree of dissociation of the salt, that is, with the number of metallic ions present in the solutions, although the undissociated molecule also seems to have some influence, and a salt which is dissociated with difficulty may in some instances make up for this drawback by the more intense toxicity of the metal. The most widely used metallic antiseptics are the mercurial salts, but silver, copper, zinc and other metals are also used as antiseptics.

Almost incredibly small quantities of some of the metals have been found to be rapidly fatal to some of the algæ, the bacteria, and the infusoria. Thus one part of the perchloride of mercury in one million parts of water kills spirogyra, one of the simpler algæ, and water distilled from copper vessels or in which small pieces of copper foil have been suspended is rapidly destructive to many lower organisms. Silver is less active and lead still less so. The amount of copper in the solution is too small to be recognized by any chemical test. This so-called "oligodynamic" action of metals, which was first obtained by Naegeli, and which has been confirmed by other observers, indicates that certain lower organisms are much more sensitive to the action of copper, and probably of other metals, than the more highly organized plants and animals.

The salts of the heavy metals are often only slowly **Absorbed.** Mercury is again an exception, but even mercury does not induce general symptoms until many hours after its administration. The other metals given by the mouth pass through the alimentary canal for the most part unabsorbed, but it seems probable that a small proportion of most of the metals finds its way into the blood. At the same time there is no question that the great proportion of most of the metals passes through unabsorbed, and is devoid of any effect except from its local action. Little is known regarding the form in which the metals are absorbed, but it is not unlikely that they are taken up in insoluble forms by the leucocytes and thus carried into the tissues. Iron seems to be the only metal which is absorbed intracellularly. When there is any lesion of the stomach and intestine, and particularly when the salt itself induces irritation and congestion, much more of the metal is taken up than by the normal epithelium. But even in the most favorable circumstances little of the metal is absorbed, and in acute poisoning the symptoms arise from the local irritation and corrosion and only to a smaller extent from the general action.

If the absorption of the metals is slow, their **Excretion** progresses even more gradually, and repeated administration leads to their accumulation in the tissues and thus to chronic poisoning. The metal seems to leave the blood very rapidly, and to become stored up in various organs, chiefly the liver, to a less extent the spleen, kidney, and bone marrow. While some of the metal is deposited in the liver and other organs, another part is excreted, for the most part along the alimentary

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tract. Thus it is found in the saliva and the secretions of the stomach and small intestine and, to a much larger extent, in the cecum and in the large bowel; in some cases the excretion is limited to the large bowel, a strict line of demarcation being formed by the ileo-cecal valve. A comparatively small amount escapes with the urine except in the case of mercury. Some metals have been detected in very small quantity in the milk, and there is reason to suppose that traces are eliminated by the other cutaneous secretions.

The **General Action** of the heavy metals in man is often elicited only by their prolonged ingestion, but it has been studied in animals by the intravenous or subcutaneous injection of such preparations as the double salts, which do not precipitate the proteins and slowly liberate the metal or its oxide. The ordinary salts cannot be used, because the precipitated albumin of the blood causes embolism, and this obscures the symptoms. The symptoms of acute metallic poisoning elicited thus in animals generally resemble fairly closely those of chronic poisoning in man.

Even when the heavy metals are injected into the blood in considerable quantity, the symptoms are often late in appearing, in the case of aluminum only after several days, so that the slowness of the absorption from the intestine is not the only factor in the delay in the onset of the intoxication.

The general symptoms of metallic poisoning, as distinguished from those due to the local action at the point of application, arise chiefly from the central nervous system, and from the excretory passages—the alimentary canal and the kidney. Metallic poisoning always induces disturbance of the **Stomach and Intestine**, manifested by loss of appetite, pain and discomfort in the abdomen, nausea, vomiting, and purging. In some cases no lesion of the canal is observed post mortem, but in the great majority congestion and swelling of the mucous membranes of the stomach and intestine are seen, or the whole surface may be covered by a diphtheritic membrane composed of necrosed cells and inflammatory exudate. Beneath this, hemorrhages occur, and if the animal lives long enough, ulcers are formed, so that the whole condition can scarcely be distinguished from that of dysentery. Some metals act strongly on the mouth and induce salivation, which is one of the earliest features of mercury poisoning. The lining membrane of the mouth becomes congested and inflamed, and numerous shallow ulcers are formed in it.

The heavy metals thus seem to have a specific action along the alimentary tract quite independent of the local action induced when they are swallowed, and apparently arising from their excretion along it. One or two metals, notably lead, cause constipation and colic when they are absorbed into the blood, but under certain circumstances they too induce purgation.

Another organ which suffers from the circulation of metals in the blood is the **Kidney**. Comparatively little of the metal is excreted in the urine, but it is found that most of this class acts as diuretics in small quantities. Somewhat larger doses irritate the renal epithelium,

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and albumin appears in the urine, along with casts, and, in severe cases, blood cells and hemoglobin. If this irritation of the secretory cells be long continued, it sets up a secondary inflammation of the interstitial tissue, and cirrhosis of the kidney results.

The **Circulation** is differently affected by different metals. The heart is often weakened only in the last stages, and it is impossible to determine how far its failure is due to direct action, and how far to the disorder of the nutrition. The blood-pressure invariably falls toward the fatal issue of the intoxication, and as a general rule, a slow fall is observed from the beginning. This fall in blood-pressure may doubtless be induced by different factors in the different forms of intoxication, but there is no question that it is partly due to the dilatation of the vessels of the intestines and stomach from the inflammation of these organs. In acute general poisoning in animals, many of the metals cause a great fall of blood-pressure, which is ascribed to their paralyzing the walls of the capillaries.

The general malnutrition from the gastro-intestinal action renders it impossible to determine whether the metals alter the metabolism of the body through directly affecting the cells, but it is not improbable that this is the case, for the loss of weight is often too rapid to be explained by the starvation alone.

The **Central Nervous System** is always affected more or less by the presence of the metals in the blood. As a general rule, the symptoms are a mixture of those of stimulation of certain divisions with those of paralysis of others. Several metals induce disturbance of the psychical centers, manifested in delirium, hallucinations and mania, or in stupor and coma. Convulsions of all forms indicate that the motor areas of the brain, the basal ganglia and the spinal cord are affected; thus epileptiform convulsions, chorea, clonic and tonic spasms occur from metallic poisoning. In several instances actual lesions of the brain cells have been shown to be caused by the ingestion of the metals. They often cause general weakness, or paresis of certain groups of muscles, and in addition to their specific action on the nervous centers, they may induce peripheral neuritis (lead).

Therapeutic Uses.—In therapeutics only mercury and iron are largely employed for their effects after absorption, while the others have a more or less extensive use for their local effects as astringents, irritants, caustics or styptics. Iron is not prescribed for its general action on the organs, but to supply the place of food-iron in the formation of hemoglobin. Mercury is used for its specific effect in syphilis, and some of its preparations are diuretics.

Metallic compounds are widely used by local application as astringents and antiseptics. Their various uses for these purposes will be considered under individual metals.

In regard to the arrangement of the metals, no strictly scientific order is perhaps possible yet. Iron will be considered first, as it stands in a class by itself owing to its physiological importance. Copper, zinc and aluminum resemble one another in being used therapeutically mainly for external application or as emetics. Lead and silver have close simi-

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larities in their local actions and to some extent in their liability to produce chronic poisoning. By leaving mercury to the last of the more important heavy metals, the trypanocidal remedies, mercury, bismuth, antimony and arsenic are brought into juxtaposition.

I. IRON

Iron is essential to the life of many, probably all, forms of protoplasm. In the vertebrates most of the iron is contained in the hemoglobin of the blood, a fact which, until recent years, has tended to obscure the importance of it in other tissues. Apart from the hemoglobin in the circulating red blood corpuscles, iron occurs not only in the organs concerned with the formation and destruction of red cells but in the tissues generally. The iron found in the blood plasma is concerned with the transport of this element through the body. Traces of iron exert a marked catalytic activity upon biological oxidations and constitute an essential part of the oxidases and other enzyme systems. Cytochrome, which may play an important part in oxidative processes, contains iron. From its presence both in hemoglobin and in other compounds, iron appears to play a part of the first importance in the oxidative processes of the body. In the invertebrates, in many of which no corresponding compound exists in the blood, considerable amounts of iron are found in the tissues, and there is no question that throughout the animal kingdom iron is essential to living matter, quite apart from its special relation to the blood in the vertebrates. It is also necessary for the development of the lower vegetable forms, and in its absence the higher plants fail to form chlorophyll, although iron is not actually contained in the latter, as it is in hemoglobin.

The iron combinations vary in the readiness with which they liberate the iron ion and therefore in the facility with which they react with such reagents as ammonium sulfide or potassium ferrocyanide; the more dissociable salts, such as the chloride or acetate, are sometimes known as "inorganic iron" while compounds such as hemoglobin, which do not dissociate the iron ion, are termed masked or "organic" iron; between these two extremes there lie many intermediate forms, which react slowly to the sulfides and other tests.

The dissociable iron salts precipitate proteins from solution and thus act as astringents or irritants according to the concentration in which they are applied; but iron has no specific poisonous action on living matter such as is possessed by mercury or antimony, and the irritation induced by such salts as the perchloride arises from the acid constituent and not from the metal. The less dissociable compounds, such as the double salts and "organic" iron, do not precipitate proteins, and are therefore neither irritant nor astringent as long as they maintain their original form and are not decomposed into simple salts.

Pharmacological Actions.—Inorganic iron compounds, of which the perchloride may be taken as a type, have an astringent, metallic, or often acid taste, but in ordinary doses induce no further symptoms. If swallowed in large quantities, they cause pain and uneasiness in the

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stomach, nausea, vomiting and often purging, with all the ordinary symptoms of acute gastro-intestinal irritation. General weakness and even collapse may be induced, but are manifestly secondary to the gastric and intestinal effects, and no symptoms which can in any way be attributed to the absorption of iron have been observed in either man or animals.

The prolonged use of inorganic iron is frequently followed by some dyspepsia and by constipation and colic, which are obviously due to the continued astringent action on the stomach and bowel. Other symptoms observed occasionally are blackness of the teeth and tenderness in the gums, which may be due to the acid contained in many iron preparations; the blackening of the teeth has been supposed to be due to the tannic acid of the food precipitating the inky black tannate of iron, or to the sulfide of iron being formed by the action of the hydrogen sulfide present in carious teeth.

The **General Action** of iron is obtained only by the intravenous injection of double salts, such as the tartrate of iron and sodium, which do not coagulate the blood and at the same time are capable of freeing the iron ion in the tissues. Such salts as the ferrocyanides or ferricyanides, on the other hand, leave the body unchanged, and the iron ion is not liberated, so that no iron symptoms are induced. In mammals the symptoms of iron poisoning are often very late in appearing, and begin with some acceleration of the breathing, which later becomes slow and dyspneic; vomiting and diarrhea often follow and blood is sometimes seen in the evacuations of the stomach and bowel. Increasing weakness is followed by central paralysis and death, accompanied by weak convulsive movements. The heart seems little affected. Post mortem, the mucous membranes of the stomach and intestine are swollen and congested, and often contain numerous small blood extravasations. Repeated injection of small quantities of the citrate of iron induces congestion of the kidney and the appearance of casts and albumin in the urine.

Amount and Distribution of Iron in the Body.—An approximate estimate of the total amount of iron in the body can be obtained in the following way. Assuming the blood volume to be one-twelfth of the body weight, an adult man weighing 70 kilograms will possess 5.8 liters of blood. Of that blood, hemoglobin forms about 15.6 per cent, which would make the total amount of hemoglobin in the blood to be about 900 grams. Since the iron content of hemoglobin is 0.335 per cent, the total blood would, therefore, contain about 3 grams of iron. As only about two-thirds of the total iron in the body is contained in the hemoglobin, the total iron content of the body would be about 4.5 grams. In spite of its great physiological importance in the body, the total amount of iron is small, comprising only about 0.006 per cent of the body weight.

Human plasma contains about 0.050 to 0.180 mg. of iron per 100 cc. This may be increased in pernicious anemia and decreased during periods of active regeneration of the erythrocytes. Muscle hemoglobin contains about 7 per cent of the total iron in the body. This iron as well as the so-called parenchyma iron of the tissues is not available for hematopoiesis. On the other hand, the iron which is stored in the reticuloendothelial cells of the liver, spleen, kidney and bone marrow is transformed into hemoglobin as needed.

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Iron in the Food.—Apart from the endowment of iron which the child receives at birth, all the iron in the body must be derived from the food. And as the proportion of iron to the body weight, especially after the first year of life, remains under normal conditions of health remarkably constant, it is clear that iron must be absorbed from the food in amounts sufficient to keep pace with growth. Plants take up iron from the soil and build it up into highly complex organic compounds. All natural vegetable foods contain more or less iron. Parsley, watercress, spinach and beans contain relatively high amounts; potatoes, wheat and most fruits contain relatively little. Animals derive their iron from the complex iron compounds of vegetables, and animal tissues contain iron in varying amounts. Liver, spleen, and kidney contain a relatively high percentage of iron, muscle contains less. Milk contains about 1 mg. per liter. The daily intake of iron in the food varies from 10 to 80 mg.

The iron in the food is required chiefly for the formation of hemoglobin. Red blood corpuscles are continually being removed from circulating blood and destroyed while new red cells, made in the bone marrow, replace them. The iron necessary for this formation of new hemoglobin is derived in small part only (about 10 per cent) from the food; the remainder is obtained from the iron derived from the destroyed hemoglobin which is retained by the tissues, particularly by the reticulo-endothelial system.

The daily iron requirement of an adult male is about 5 to 8 mg. Women may require two or three times this amount to compensate for the loss of iron in the menstrual blood. During pregnancy also their requirement is about 20 mg. daily.

Absorption and Excretion.—Iron in the food exists as more or less complex organic compounds, which do not give the reactions of free iron ions. Apart from occasional traces of iron in drinking water, the iron in the diet consists entirely of non-ionizable iron. The large molecular compounds containing iron which are present in the food have to be reduced by digestive processes into smaller and more diffusible molecules before they can be absorbed.

Though at one time it was suggested that iron can only be absorbed in organic combination and not as inorganic ionized compounds, recent investigations have proved conclusively that inorganic iron compounds can be readily absorbed. Indeed, it is now believed that even the food iron may first have to be changed into ionized iron before it can be absorbed.

The site of absorption of iron from the alimentary canal has been determined by histological methods, reagents being used which color most forms of iron but leave the hemoglobin unaffected. When animals are given iron preparations, and are then killed and the mucous membrane stained by these reagents, the mucous membrane of the stomach and of the greater part of the small intestine gives no coloration, but the epithelium of the duodenum and of the upper part of the jejunum (the contents of which are acid in reaction) is found to contain numerous granules of iron. In the more distant parts of the intestine where the reaction becomes neutral or alkaline, the iron forms insoluble phosphates,

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carbonates or more complex salts, which are not absorbed. When there is very little iron in the food, the body is extraordinarily conservative of its iron and picks up the slightest traces of iron from the food. On the other hand, if excessive amounts of iron are given in the food, and provided that this does not damage the intestinal epithelium, the intestine soon ceases to absorb it. There must, therefore, be some mechanism which regulates the absorption of iron in accordance with the needs of the body, and the suggestion is that, when the body is plentifully supplied with iron, the epithelial cells of the intestine share in the richness and fail to absorb iron; but when the body is poorly supplied, these cells, being also deficient in iron, absorb the metal more readily. While during growth or in iron deficiency, iron may be rapidly absorbed, in the adult, only minute traces of iron are taken up from the food, the iron obtained from the destruction of red blood corpuscles being used over again for the formation of new hemoglobin.

The amount of iron normally excreted in the urine is negligible, most of it being excreted in the feces which normally contains 10 to 50 mg. of iron daily. It was formerly believed that iron was excreted from the body through the colon, but the validity of this view is now questioned. The iron appearing in the feces represents that portion of the iron in the food which has escaped absorption. The iron content of the body is regulated apparently by control of its absorption rather than its excretion.

Fate of Iron in the Body.—Iron absorbed from the food probably undergoes changes in the intestinal epithelium, and the resulting combinations are given off gradually into the blood, and taken up by the liver. Blood destruction takes place principally in the spleen and the iron containing compounds derived from hemoglobin are given off gradually from the spleen and taken up and stored in the liver. From this organ iron compounds are again given up to the blood and utilized over again by the bone-marrow in the formation of hemoglobin of new cells. The store of iron in the liver, spleen and other tissues can be mobilized when necessary to form hemoglobin.

To sum up the main facts of iron metabolism, so far as they are known, iron occurs in the food in the form of more or less complex organic compounds which have to be disintegrated into smaller molecules, possibly even to inorganic compounds, by the digestive processes before they can be absorbed. The value of a particular food as a source of iron depends upon its iron content and upon the ease with which it can be disintegrated. These simpler compounds, as well as iron salts like ferrous chloride, are taken up by the epithelial cells of the upper part of the small intestine, probably as ferrous ions. They are then gradually given off into the blood and stored in the liver and spleen. The fate of iron compounds liberated from the liver and spleen into the blood depends upon the needs of the body. What iron is required for the formation of the hemoglobin is taken up by the bone marrow. The body readily absorbs iron when necessary, *e. g.*, during growth. In the healthy adult, however, under normal conditions, only minute amounts of iron are absorbed and excreted; practically all the iron liberated by

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the breakdown of hemoglobin is retained in the body and used over again for the manufacture of hemoglobin.

Iron in Experimental Anemias.—A large number of observations have been made on animals rendered anemic in various ways with a view to observing the factors concerned in blood regeneration and the best methods of treatment of anemias. The use of labeled (radioactive) iron has been particularly useful in following the course of iron through the body and its rôle in erythropoiesis. By the use of iron-poor diets in rats it has also been shown that copper and possibly other heavy metals are also essential for hemoglobin formation. However, it is now agreed that the results obtained from the study of experimental anemias in the lower animals can only be tentatively applied to the treatment of anemia in man. Thus most patients with hypochromic anemia seem to require no added copper but in certain cases, particularly in infants, the addition of copper along with iron seems to lead to greater increases in the hemoglobin level than is the case without the added copper. In experimental animals also there is little obvious distinction between the effects of ferrous and ferric iron on the rate of its utilization. On the other hand, in the human, experiments, in which labeled (radioactive) iron was administered, have demonstrated that ferrous iron is more readily absorbed than is ferric iron.

Therapeutic Uses.—It is convenient to consider, first, the diseases in which iron is of value and, second, the best methods of administering it.

Iron is generally useful, and often strikingly successful, in the treatment of all forms of hypochromic microcytic anemia with the exception of Mediterranean or Cooley's anemia. Such anemia is characterized by a low hemoglobin content of the red cells, an abnormally small cell and a diminished color index. It is encountered in conditions where the intake of iron has been deficient, where there has been an excessive loss of iron as in hemorrhage or excessive menstrual flow, in infancy and pregnancy where the demand for hemoglobin is increased, in hookworm disease, in the so-called idiopathic hypochromic anemia and in chlorosis. Until recent years iron found its chief sphere of utility in the treatment of *chlorosis*, in which its reputation is attested by the old saying, "qui nescit Martem, nescit artem," a survival of the astrological association of iron with the planet Mars. Owing to more hygienic methods of living and more judicious dieting, chlorosis has become an increasingly rare disease in nearly all countries during the last quarter of a century. Chlorosis is characterized by a relatively slight reduction in the number of red cells but by a marked reduction in the amount of hemoglobin in each. The effects of iron are seen in an increase of the hemoglobin in the blood, while the number of corpuscles may also show a considerable increase. A number of symptoms which are secondary to chlorosis, and which are often more prominent than the original disease, are also relieved or entirely removed by iron. Thus gastric catarrh, amenorrhea, breathlessness or edema may disappear under it, but in these cases the improvement is due to the increased hemoglobin and not to the direct action on the stomach, uterus or the circulation. Many cases of chlorosis recover without inorganic iron under hygienic conditions, such as rest,

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and particularly when foods rich in iron are prescribed, this being exactly what is to be expected on the theory that inorganic iron merely takes the place of the deficient food-iron.

The effects of iron therapy in other forms of hypochromic microcytic anemia are as dramatic as in chlorosis. About the fifth to tenth day after the institution of iron therapy, there is an increase in the reticulocytes and the hemoglobin content and red cell count increase. The hemoglobin regeneration after an initial lag of several days may continue at a rate of 0.25 gram per day until normal values are approached when the rate of regeneration becomes slowed. Administration of iron to a normal individual does not stimulate the production of hemoglobin since the metal has no effect on erythropoiesis but merely supplies an essential element for the hemoglobin molecule.

Symptomatic improvement accompanies the increase in hemoglobin content which follows the administration of iron. The appetite improves, strength is regained, the skin resumes its normal color and resiliency, the papillæ of the tongue are restored, the enlarged spleen recedes to its normal size and the brittle concave nails are replaced by normal structures.

The therapeutic response to adequate doses of inorganic iron is much more rapid than that observed when the diet alone is depended upon to supply the deficiency of iron. This difference in the effects of the iron of the food and of the inorganic preparations may be due to the fact that food-iron is always accompanied by a large amount of colloid material, which may materially delay its absorption, while inorganic iron, on the other hand, is much less completely enveloped and may be more easily absorbed. In addition, the iron preparations are given in much larger amounts than the food-iron. When 10 mg. of food-iron are taken per day, only a small proportion (*e. g.*, 5 mg.) may be absorbed, and this may be insufficient to supply the needs of the body, but if some hundreds of milligrams of inorganic iron be added, the proportion absorbed will be amply sufficient. The same effect might be obtained by the same amount of food-iron, but this is only to be obtained by giving more food than can be digested.

Administration of Iron.—Iron has been administered in a great variety of combinations but it is highly probable that in the near future the number of iron preparations will be drastically reduced. The preparations most commonly employed are (1) metallic or elementary iron; (2) ferrous salts such as ferrous carbonate, sulfate, lactate, gluconate, or iodide; (3) ferric salts, such as ferric chloride and (4) complex compounds such as iron and ammonium citrate.

Complex organic preparations, such as albuminates or hemoglobin itself, have not proved so effective as inorganic iron either in experimental or human anemias. Probably the larger molecules must be broken down by the digestive juices before absorption, and as sources of iron they do not seem to provide a short cut to hemoglobin formation. Soluble ferric salts are more astringent and irritant than the corresponding ferrous salts. They are more liable to produce dyspepsia and consti-

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pation and moreover they must probably be reduced to ferrous compounds before they are absorbed. Though they will act efficiently, they possess disadvantages compared with ferrous salts, and clinical opinion has steadily shown a preference for ferrous salts. This preference, as already indicated, is supported by the recent work which has shown that ferrous salts are more readily utilized in the human than are the corresponding ferric salts.

The most popular iron salt used in the treatment of anemia is ferrous sulfate, which is prescribed in the form of coated tablets. Ferrous lactate and gluconate are less apt to produce gastro-intestinal irritation and may be used instead of the sulfate. Ferrous carbonate is the active constituent of the classic Blaud's pills introduced by Pierre Blaud in 1831 and prepared by mixing ferrous sulfate and potassium carbonate. Ferrous carbonate is unstable, being slowly transformed into ferric hydroxide. Oxidation is to a certain extent prevented by the addition of sugar as in the Ferri Carbonas Saccharatus. In Pilula Ferri Carbonatis, ferrous carbonate is formed in the pill mass and is to a considerable extent thus prevented from oxidation. Being insoluble, the carbonate is less irritant to the stomach, where it is converted into the soluble chloride. The fact that it has to be converted into a soluble chloride before absorption suggests that it would be less effective in anemias complicated by achlorhydria, though even then it may be rendered soluble by organic acids in the stomach.

The same remarks apply to reduced iron, which consists mainly of metallic iron with a varying amount of iron oxide. It is partly converted in the stomach into ferrous chloride, a conversion which is necessary for absorption.

As iron is absorbed in the form of ferrous chloride and as this salt undergoes no change in the stomach, it is also a suitable salt for administration. It may be prepared in syrup and administered in milk and is a useful preparation for infants. The double salts of iron, such as the Ferri et Ammonii Citras, are soluble but do not give free iron ions. They are therefore not astringent or irritating and do not disturb digestion. They are effective in anemia if given in sufficient doses.

Iron in the form of the green (ferrous) iron and ammonium citrate may be given by intramuscular injection in doses of 0.06 gram two or three times daily. However, this route of administration is potentially harmful and is justified only on the rarest occasions.

The salts of ferric iron are also employed externally as **styptics.** The perchloride may be used for this purpose and acts by precipitating the proteins of the blood and thus obstructing the flow of blood from the wounded vessel. This treatment is of value only for oozing from capillaries or small arterioles and iron must be brought into immediate contact with the bleeding point. The tincture of ferric chloride is used as an astringent for application to the throat.

Dosage.—In the treatment of hypochromic anemia, doses of the various preparations of iron must be used which are exceptionally large considering the fact that there is less than 5 grams of iron in the entire

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body. In moderately severe anemia the following amounts of the various compounds are administered in divided doses daily:

Preparation	Daily dose in grams	
	Adults	Infants
Reduced iron	2–6	
Ferrous sulfate	1–2	0.4
Iron ammonium citrate	4–8	0.6
Ferrous carbonate	2–4	
Ferrous chloride	0.5–1	0.2

The larger doses cited in the above table are indicated in cases of chronic anemia with achlorhydria. When the anemia is due to chronic blood loss and when gastric secretion is normal, smaller amounts are effective.

Iron salts should be administered shortly after meals to reduce gastric irritation. A tolerance may be induced by starting with a small dose and gradually increasing it.

For prophylactic purposes, as in pregnancy, smaller doses than are indicated in anemia suffice. In patients with chronic anemia the administration of small doses (0.2 gram ferrous sulfate daily) may have to be continued after the blood has been restored to normal.

Preparations

U. S. P.

Ferri et Ammonii Citrates, thin garnet-red scales with a salt, iron taste, soluble in water and containing 17 per cent of iron. Dose, 1 gram.

Ferri et Ammonii Citrates Virides; contains about 15 per cent of Fe. Dose by intramuscular injection 0.06 gram.

Ferri Sulfas, ferrous sulfate ($FeSO_4.7H_2O$), large, pale, bluish-green crystals with a saline, astringent taste, soluble in water, insoluble in alcohol, and unstable in moist air. Dose, 0.3 gram.

The sulfate of iron is very astringent, though less so than the ferric salts.

Ferri Sulfas Exsiccatus, exsiccated ferrous sulfate, a grayish white powder containing not less than 80 per cent of anhydrous $FeSO_4$. Dose, 0.2 gram.

Ferrum Reductum, reduced iron, a very fine, grayish-black, lusterless powder, without taste, insoluble in water or alcohol, soluble in acid. It consists of metallic iron, with a small amount of the oxide. Dose, 0.5 gram.

Pilulæ Ferri Carbonatis, ferruginous or chalybeate pills, Blaud's pills, are prepared by the action of ferrous sulfate and carbonate of potash with the addition of sugar, althea, tragacanth, and glycerin. Each pill contains not less than 60 mg. of $FeCO_3$. Dose, 5 pills.

B. P.

Ferri Carbonas Saccharatus, an olive-brown, slightly hygroscopic powder, partially soluble in water and containing not less than 50 per cent of $FeCO_3$. Dose, 0.6 to 2 grams.

Ferri et Ammonii Citras, dark-red transparent scales, with an astringent taste, deliquescent in moist air, freely soluble in water. Contains about 21 per cent of iron. Dose, 1.3 to 2.6 gram.

Ferri et Quininæ Citras, thin, greenish-yellow scales, with a bitter, chalybeate taste, deliquescent in moist air, freely soluble in water. Contains about 15 per cent of anhydrous quinine and about 13 per cent of iron. Dose, 0.3 to 1 gram.

Ferri Subchloridum Citratum, a buff-colored powder with an acid astringent taste, freely soluble in water. Dose, 0.2 to 0.3 gram.

Ferri Sulphas, as in U. S. P. Dose, 0.06 to 0.3 gram.

Ferri Sulphas Exsiccatus, as in U. S. P. Dose, 0.03 to 0.2 gram.

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FERRUM, metallic iron.

FERRUM REDACTUM, a fine grayish-black powder, insoluble in water, and containing not less than 80 per cent of metallic iron. Dose, 0.06 to 0.6 gram.

LIQUOR FERRI PERCHLORIDI, contains 15 per cent of $FeCl_3$. Dose, 0.3 to 1 mil.

PILULA ALOES ET FERRI, contains ferrous sulfate, aloes, syrup and flavoring agents. Dose, 0.25 to 0.5 gram.

PILULA FERRI CARBONATIS, prepared by action of ferrous sulfate and sodium carbonate, with tragacanth, acacia and liquid glucose as excipients. Dose, 0.3 to 2 grams.

SYRUPUS FERRI IODIDI, contains 5 per cent of FeI_2. Dose, 2 to 8 mil.

SYRUPUS FERRI PHOSPHATIS COMPOSITUS, Parrish's food, chemical food, contains phosphates of iron, calcium, sodium and potassium. Dose, 2 to 8 mil. (30 to 120 min.).

SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA, Easton's syrup; 60 min. contain about $\frac{1}{2}$ gr. of iron, $\frac{4}{5}$ gr. of quinine sulfate and $\frac{1}{60}$ gr. of strychnine hydrochloride. Dose, 2 to 4 mil. (30 to 60 min.).

SYRUPUS FERRI PHOSPHATIS CUM STRYCHNINA, syrup of ferrous phosphate with strychnine, Easton's syrup without quinine. Dose, 2 to 4 mils.

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II. COPPER

Copper seldom gives rise to poisoning, and has been less frequently used in medicine than many of the other heavy metals, though recent researches have indicated that it may have a use in the treatment of certain anemias. The soluble salts precipitate proteins from solution, and are therefore astringent when applied to the mucous membranes and to wounded surfaces. In larger quantities they are somewhat irritant and corrosive, although less so than mercury.

Symptoms.—The copper salts have a harsh, metallic, astringent taste, and when swallowed in some quantity cause nausea, salivation, and vomiting. The most of the salt is thus removed, and no further symptoms are observed. Large quantities, however, induce corrosion of the walls of the stomach and intestine, and give rise to violent vomiting and purging, the copper giving a blue or green color to the vomited matter and the stools, and blood appearing in them later from the corrosion of the mucous membrane. Violent pain in the abdomen is complained of, and the usual symptoms of acute corrosive poisoning may follow: collapse, with weak pulse and respiration, headache, giddiness, unconsciousness, delirium, coma, convulsions, and paralysis.

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These may prove fatal in a few hours, but more frequently the patient lives for several days to sink eventually from exhaustion.

Toxicology.—The nausea, vomiting and purging of acute copper poisoning are due to the local effect on the mucous membranes of the stomach and intestine. In fact, although some copper is absorbed in these cases, there is no reason to suppose that any of the acute symptoms are due to it, for they are all induced by other poisons which act only as gastro-intestinal irritants.

The occurrence of **Chronic Copper Poisoning** in man has not been established. In copper- and brass-workers, gastro-intestinal catarrh, or colic and diarrhea, occur occasionally and are ascribed to the copper swallowed or inhaled in the course of their occupation. The dust inhaled may similarly cause laryngeal irritation and bronchitis. The skin and hair often have a greenish tint, and a green line on the teeth, just where they enter the gums, is known as the copper line; but it is believed that these are due largely to the copper dust deposited on the skin, hair and teeth, and not to the excretion of the metal. Local paralysis, anemia, tremor, emaciation and cutaneous eruptions are said to have followed these symptoms in some cases, but it may fairly be doubted whether these symptoms are really due to the copper or to the lead, arsenic and other poisons often associated with it. Furthermore, copper has been taken in the form of the metal, or of its soluble salts, for prolonged periods without any symptoms being elicited except those of slight intestinal catarrh and some nausea.

In animals the general action may be elicited by the injection of slowly dissociated salts, such as sodium-copper tartrate, into the blood or subcutaneously. In mammals the intravenous injection of copper does not cause vomiting, but the locomotion soon becomes slow, clumsy and weak, and later complete paralysis of the spontaneous movements follows. The heart and respiration seem equally involved, but the respiration ceases somewhat earlier than the heart. When an animal survives longer, violent, sometimes bloody, diarrhea is generally induced by copper, as by most of the other heavy metals. The animals lose flesh rapidly, and refuse food, and the urine often contains albumin and blood. Similar results are obtained in rabbits when copper is given by the mouth, as this animal is incapable of rejecting the poison by vomiting. In the dog, on the other hand, poisonous doses are removed by vomiting when they are given by the mouth.

Absorption.—Copper is absorbed from the intestine, for large quantities have been found in animals fed on it for some time; a large proportion of the metal is absorbed when small doses are given, but the proportion lessens as the dose is increased. It also passes into the blood from other mucous surfaces and from wounds. The copper absorbed from the intestine is lodged chiefly in the liver, less in the spleen, kidney, and thyroid. It is excreted especially by the intestinal tract, to a less extent in the urine. Traces have been found in saliva, bile and milk and it is said to pass from the mother to the fetus in utero. Copper is found in small quantities in these organs and secretions in man and in animals that have not been treated with it, but in a much larger amount after prolonged administration.

Copper is found as a normal constituent of the blood in many of the invertebrates, in which it performs the same function as the iron of the hemoglobin in the vertebrates. It has been detected in one of the pigments of birds' feathers and it may be regarded as a normal constituent in the tissues of mammals. It is probable that traces of copper play a rôle in certain enzyme systems. Oysters and other animals take it up in large quantities when they live in water rich in copper, and apparently are not injured by it, while on the other hand the traces of copper contained in the water distilled in copper vessels is sufficient to destroy tadpoles and tubifex, one of the annelid worms. Traces of copper,

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added to the water in which they live, destroy some of the simpler algæ, and the parasites of the grape vine, potato, apple and other plants are killed by spraying the plants with copper; yeast ceases growing in a 0.02 per cent solution, while the moulds seem to be almost immune to its action.

Therapeutic Uses.—The principal salt of copper used in therapeutics is copper sulfate (blue vitriol). The chloride of copper is more irritant and hence not used. Cupric citrate, on the other hand, is only sparingly soluble and is used as an astringent in the form of a 5 or 10 per cent ointment for application to the eye. Copper sulfate was formerly used internally as an *emetic*, being given for this purpose in about 1 per cent solution. It acts promptly, and does not leave much depression and nausea, and for this reason is unsuitable as an expectorant. In *phosphorus poisoning* it is especially valuable, as in addition to causing evacuation of the stomach, the metal is deposited on the particles of phosphorus and prevents their absorption. As an emetic in other conditions, zinc sulfate is preferable, as it causes less irritation of the stomach should vomiting not take place. Emetics, however, are infrequently used in modern medical practice, resort being made to the stomach tube as a more effective method of emptying and washing the stomach where this is desirable as in cases of poisoning.

Externally copper sulfate is used as an *astringent* for irrigation of the urethra, and occasionally as a lotion in ulcers and wounds; for this purpose it is employed in 1 per cent solution. The solid crystals are sometimes used to touch exuberant granulations for their astringent and corrosive effect.

Small quantities of copper sulfate have recently been used to destroy the algæ which grow in reservoirs and often give the water a disagreeable odor and taste. The proportion of copper required for this purpose is about one part in a million or sometimes in fifty millions; this treatment does not render the water deleterious to man, for much larger quantities of copper have been taken constantly without injury. Copper sulfate has also been used as a fungicide for application to the skin in the treatment of epidermophytosis.

A new physiological function for copper has been elucidated by recent researches on experimental anemias. Experiments on induced anemias in laboratory mammals indicate that copper does not affect the absorption or storage of iron but facilitates the formation of hemoglobin, in spite of the fact that copper is not itself a constituent of hemoglobin. Copper is widely distributed in food material, green vegetables and liver being especially rich in it. On the analogy of experimental anemias the amounts of copper needed is very small, only a few milligrams per day, which would be amply supplied by an adult mixed diet. On the other hand, milk, especially cow's milk, is low in copper as well as in iron content, and it is possible that children fed on cow's milk may suffer from a deficiency of both copper and iron. Indeed results have been published to show that anemia in children may be cured by simultaneous administration of iron and copper more rapidly than by iron alone, and that in a certain proportion of cases copper is necessary for the cure. However, as indicated already, in the anemias encountered in the adult

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there is no indication that a deficiency of copper plays any part in their pathogenesis. In general there is no indication for the administration of copper in anemia except in some cases of anemia in infants who have subsisted solely on a milk diet. The dose of copper sulfate in such cases is about 3 mg. of copper sulfate daily given orally in milk or fruit juices.

Copper forms a very stable compound with chlorophyll, and traces of copper salts are sometimes used to give a bright green color to preserved green vegetables. No harmful results have been proved to occur from this practice so long as the copper is in organic combination and the amount added is small.

Copper has recently been shown to exert a neutralizing effect on the lethal action of hydrocyanic acid in rabbits. It is assumed that the copper counteracts the inhibiting effect of the HCN on the catalase of the erythrocytes (Clemedson).

In cases of **Poisoning** with copper salts, the stomach generally rejects the metal by vomiting and no emetic is required. Non-corrosive compounds may be formed by giving milk, egg, or other forms of albumin, tannic acid, magnesia, or ferrocyanide of potassium. Morphine may be required for the pain, ice to stop the vomiting.

Preparations

Cupri Sulfas (U. S. P., B. P.) ($CuSO_4.5H_2O$), large, transparent, deep blue crystals, without odor, but with a nauseous, metallic taste, soluble in water, scarcely so in alcohol. Dose, B. P., 0.016 to 0.12 gram; as an emetic, 0.3 to 0.6 gram.

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III. ZINC

The effects of zinc resemble those of copper closely except that salts of zinc are, in general, much weaker in their effects than the corresponding salts of copper. Like copper, the soluble salts precipitate proteins and therefore possess an astringent action, or in large quantities act as irritants and corrosives. The sulfate is the soluble salt most commonly used in medicine, but the chloride, which is used only as a caustic and disinfectant, has frequently given rise to corrosive poisoning. Zinc also plays a rôle in the animal economy being a normal constituent of the pancreas and insulin (*cf.* p. 559).

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Symptoms.—The sulfate of zinc has a harsh, metallic taste, and in small doses causes nausea and vomiting, in larger quantities, violent vomiting and purging, pain in the abdomen and collapse; these symptoms are due to the local action on the stomach and intestine. The insoluble zinc oxide and carbonate are not liable to cause acute irritation. but their prolonged ingestion has given rise to dyspepsia and constipation or diarrhœa in some cases. The continued administration of zinc salts has no effects in man, except those of disordered digestion and constipation, and Lehmann could detect no effects in the dog after the administration of 155 grams of the carbonate in the course of three hundred and thirty-five days, although a considerable amount of the metal had been absorbed.

In workers exposed to zinc fumes a condition known as "*brassfounders' ague*" is occasionally met with. It is ushered in by dryness of the throat, hard cough, metallic taste, constriction of the chest, lassitude and weakness, sometimes with nausea and vomiting; muscle cramps and joint pains are often present, and later prolonged rigors and shivering are followed by a rapid acceleration of the pulse, coughing and soreness of the chest, and headache. These symptoms give place to profuse perspiration, and the patient sinks into a sleep from which he awakes in ordinary health. The attack has been attributed to the absorption of decomposition products of the proteins destroyed by the fumes of zinc inhaled; it is held that the same symptoms would arise from the fumes of other metals, but these are less volatile than zinc and are therefore seldom inhaled. A number of obscure nervous conditions have also been described as arising from zinc in workmen in brass factories and bronze-works, but it is probable that these are really due to impurities, such as arsenic and lead present in zinc ores. Instances of acute poisoning have also been reported from the use of utensils galvanized with zinc. Nausea, vomiting, diarrhea and abdominal pain are the common symptoms.

Action.—The general action of zinc can be observed only when a double salt is injected intravenously or hypodermically, as the ordinary salts precipitate the proteins of the blood when injected into a vein, and cause acute irritation when applied subcutaneously. In mammals, the intravenous injection of zinc causes vomiting and diarrhœa, weakness, tremor and paralysis of the extremities; and the stomach, intestines and heart contain small hæmorrhages. The blood-pressure seems to be but little affected, until just before death, but the pulse is slowed.

Zinc seems therefore to depress the central nervous system and to a less extent the heart and voluntary muscles, and to cause irritation and congestion of the mucous membrane of the stomach and intestine and inflammation of the kidney. The fact that vomiting occurs from the intravenous injection of zinc salts is explained by the metal inducing inflammation in the stomach.

Therapeutic Uses.—Zinc sulfate may be used internally as an *emetic*. Externally the zinc preparations, with the exception of the chloride, are used as *astringents* and *antiseptics*, the sulfate being applied in solution, the oxide and carbonate as powders, lotions, or ointments. The oxide is especially useful as an application in many skin diseases. Zinc peroxide is also used as an anti-infective for application to wounds

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(cf. p. 791). Calamine, an impure carbonate of zinc, is used in ointments and lotions as an astringent and to impart a pink color. Solutions of the sulfate or acetate are used as an eye wash (0.1 to 1 per cent) particularly in conjunctivitis caused by the Morax-Axenfeld bacillus, and as an injection (0.5 to 4 per cent) in gonorrhœa, leucorrhœa and otitis. The stearate is used as a soothing and mildly antiseptic preparation for acne, eczema and other skin diseases. Zinc sulfate is also used in conjunction with sulfurated potash (white ointment) for application to the skin.

The chloride of zinc differs from the other salts in being a powerful caustic, and is used as a paste or in pencil form to destroy malignant growths, or in chancres and gangrenous sores. It produces a white eschar and is said to be less liable to spread over the surface than potash, but penetrates the epidermis with difficulty, and it is therefore advisable to destroy this with potash or a blister before applying the caustic. It is sometimes mixed with flour or dried gypsum and water to a paste (Canquoin's paste), when a less active caustic is desired. Its use is much more restricted at the present time than formerly. Burnett's disinfecting solution (a somewhat stronger solution than the official liquor) is used to disinfect fæces and urinals, and the liquor of the pharmacopœia may be employed for the same purpose. It has frequently given rise to severe corrosive poisoning from being swallowed accidentally or suicidally.

Preparations.

U. S. P.

Zinci Sulfas ($ZnSO_4\ 7H_2O$), colorless, transparent, odorless crystals, with a harsh, astringent, metallic taste, soluble in water, not in alcohol.

Zinci Acetas, pearly crystals, efflorescent, soluble 1 part in 2–3 of water.

Zinci Chloridum ($ZnCl_2$), a white powder, or porcelain-like mass, irregular or moulded into pencils, odorless and strongly caustic, very deliquescent and soluble in water and alcohol.

Zinci Oxidum (ZnO), an amorphous white powder without odor or taste, insoluble in water.

Unguentum Zinci Oxidi, 20 per cent, in paraffin or petroleum jelly.

Zinci Stearas, a white impalpable powder, insoluble in water.

B. P.

Zinci Chloridum.

Zinci Oxidum, used in the preparation of:

- Unguentum Zinci Oxidi, 15 per cent in simple ointment.
- Unguentum Zinci Oxidi Aquosum (B. P.), hydrous ointment of zinc oxide, 15 per cent in hydrous ointment.
- Gelatinum Zinci (Unna's paste), 15 per cent in gelatine, glycerin and water.
- Pasta Zinci Oxidi Composita, 25 per cent in starch and soft paraffin.
- Unguentum Zinci Oleatis, zinc oleate ointment, consists of equal parts of zinc oleate and hydrous ointment.

Zinci Stearas.

Zinci Sulphas. Dose, 0.06 to 0.2 gram; as emetic, 0.6 to 2 grams.

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IV. ALUMINIUM AND ALUM

The chief preparations of aluminium used in medicine are the sulfate of aluminium and potassium, or alum, which has been largely used for its astringent properties; the insoluble hydroxide and phosphate which are used as antacids; and the acetate and chloride which are used as antiseptics and astringents. Alum solutions precipitate proteins in the same way as the salts of the other heavy metals, and dilute solutions have thus an astringent action, while larger quantities and more concentrated solutions act as irritants. This is more especially the case when dried alum is applied, for, in addition to its coagulating effect on the proteins, this preparation has a great avidity for water.

Symptoms.—Alum solutions have a sweetish, astringent taste, and in small quantities induce no symptoms except a feeling of dryness and astringency of the mouth and throat, and some constipation. Larger doses act as gastric irritants and cause nausea and vomiting, and, in extreme cases, purging. Even the largest quantities, however, are followed by no symptoms except those of gastro-intestinal irritation and inflammation, and the long-continued use of alum does not elicit any symptoms of chronic poisoning. The aluminium salts are only absorbed in small quantity from the stomach and intestine, so that no symptoms of general poisoning arise from the internal use of the salt. The small amount of aluminium absorbed is stored up in the liver, kidney, muscles and pancreas and slowly excreted in the bile and urine.

The suggestion that toxic effects may result from the ingestion of food cooked in aluminium vessels has given rise to much controversy and experiment. The evidence on the whole is that the amount of aluminium so introduced into the system is too small to produce any deleterious effects (Burn). Alum has been used extensively in baking powders. With any ordinary diet this could hardly lead to the ingestion of more than 60 mg. of aluminium per day, a quantity which appears to be quite innocuous. Very large amounts of aluminium taken experimentally with foods in the form of baking powders were found to produce diarrhea, but no symptoms of general poisoning have been proved to result from the ordinary use of such powders. Likewise the administration of large amounts of insoluble aluminium salts over long periods to animals or man results in no obvious symptoms of poisoning. Deaths from the ingestion of large doses are attributable to their local action on the mucosa of the gastro-intestinal tract.

Action.—Aluminium has a very remarkable general action when it obtains access to the blood. In Siem's experiments on animals, the sodium-aluminium lactate or tartrate induced a very slow intoxication, mammals never dying from the effects sooner than one or two weeks after the intravenous injection of the salts. In mammals the first symptoms appeared only after three to five days.

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and consisted of constipation, rapid loss of weight, weakness, torpor and vomiting; marked abnormalities in movement and sensation were observed later, such as tremor, jerking movements, clonic convulsions, paresis of the hind legs, anesthesia of the mouth and throat, and lessened sensation all over the body. Before death, diarrhea often set in, and albuminuria was generally present. The mucous membrane of the stomach and bowel was found swollen and congested, the kidney and liver had often undergone fatty degeneration, and hemorrhages were found in the renal cortex. Aluminium was found in the urine. Like the other members of the heavy metal series, aluminium therefore acts on the bowel and kidney in general poisoning, while many of the symptoms point to a direct action on the brain.

Uses.—Alum is used chiefly externally for its astringent properties. Its aqueous solution is used as an *astringent* gargle (1 to 5 per cent), as an injection in gonorrhea ($\frac{1}{2}$ to 1 per cent), as an astringent lotion in skin diseases (1 per cent), and for other similar purposes. Dried alum is more caustic, from its withdrawing fluid from the tissues; it has been used as an application to exuberant granulations, hemorrhoids, or condylomata, and as a styptic in bleeding from the nose or teeth.

A large number of aluminium preparations have been introduced as antiseptic astringents. Among these may be mentioned *alumnol* (naphthol sulphonate of aluminium), *salumin* (salicylate), *tannal* (tannate), *gallol* (gallate), *boral* (borotartrate), *cutol* (borotannate), *alsol* (acetate), *alkasal* (salicylate of potassium and aluminium). They are used partly in solution, chiefly as dusting powders.

Aluminium hydroxide in the form of an aqueous suspension or tablet and aluminium phosphate in the form of a suspension are widely used as gastric antacids. Aluminium hydroxide neutralizes the excess hydrochloric acid of the stomach without producing systemic alkalinization as is the case when sodium bicarbonate is used for this purpose. The aluminum chloride formed in the stomach is presumably reconverted to the hydroxide in the alkaline intestine. In addition to their antacid effects aluminium hydroxide and phosphate also exert mild astringent and demulcent actions in the stomach. Aluminium hydroxide may, by reacting with the phosphate to form insoluble aluminum phosphate, induce a phosphorus deficiency and may be used for this purpose when this is desirable, as in renal lithiasis. Aluminium hydroxide is administered in doses of 4 to 8 cc. of the 3 to 5 per cent suspension every two to four hours or one-half to one hour after meals. It is also administered by continuous drip diluted two to three times with water at a rate of about 1500 cc. per twenty-four hours in the treatment of peptic ulcer. Aluminium phosphate gel has actions and is used similarly to the hydroxide. It does not interfere with the absorption of phosphorus. It is administered in doses of 15 to 30 cc. every two hours during the active stage of ulcer.

Preparations

Alumen (U. S. P., B. P.), alum, potassium or ammonium alum ($AlK(SO_4)_2 \cdot 12H_2O$, or $AlNH_4(SO_4)_2 \cdot 12H_2O$), large, colorless, octahedral crystals, with a sweetish, strongly astringent taste, soluble in water but not in alcohol. Dose, B. P., 0.3 to 0.6 gram.

Alumen Exsiccatum (U. S. P.), burnt alum, dried alum ($AlK(SO_4)_2$, or $AlNH_4(SO_4)_2$), a white, granular powder, attracting moisture on exposure to air, soluble in water.

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GLYCERINUM ALUMINIS (B. P.), a 13 per cent solution of potassium or ammonium alum in aqueous glycerin. Dose, 2 to 4 mil.

GELATUM ALUMINI HYDROXIDI (U. S. P.), aluminum hydroxide gel, an aqueous suspension containing the equivalent of about 4 per cent of Al_2O_3. Dose, 8 cc.

GELATUM ALUMINI HYDROXIDI SICCUM (U. S. P.), dried aluminum hydroxide gel. Dose, 0.6 gram.

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V. LEAD

Lead is of negligible importance in therapeutics; its chief interest from a medical point of view lies in the frequency with which it gives rise to chronic poisoning, and in the diversity of the symptoms presented in that condition.

Solutions of lead salts precipitate proteins, and this precipitate is formed when lead solutions are applied to the mucous membranes and protects them. The metal contained in the precipitate is not destructive to the cells as in the case of mercury, so that the lead salts are less corrosive; and the salt chiefly used is the acetate, whose acid is only slightly active, so that the astringent action of the protein precipitate is the chief feature of the action. Solutions of lead nitrate are irritating and corrosive, however, because it is more readily dissociated and the nitric acid freed is itself corrosive.

Symptoms.—Lead acetate solutions applied to the skin have no effect, but mucous membranes, or exposed tissues, such as ulcers, are covered with a thin pellicle of precipitate, which serves to protect them from irritation, and thus promotes their healing. In small doses, the acetate of lead (sugar of lead) has a sweetish, metallic taste followed by a feeling of astringency, and induces no symptoms except constipation. The stools after lead are often dark in color from the sulfide formed in the intestine, but this does not seem to be the general rule. Probably little lead is absorbed from an ordinary dose of the acetate; at any rate no symptoms arise from the general action of the metal absorbed.

When very large quantities of acetate are swallowed, particularly if in a concentrated form, they give rise to the ordinary symptoms of irritant poisoning, nausea, vomiting, pain in the abdomen, violent purging or sometimes constipation, blood in the vomited matter and stools, great thirst, weakness, and collapse. In some instances in which the patients recovered from these symptoms, they subsequently suffered from chronic lead poisoning, but apart from these, nothing in the course of acute lead poisoning suggests the absorption of the metal,

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all the symptoms being obviously due to the local effects on the stomach and bowel, and to the consequent collapse.

Absorption and Excretion.—Lead is present in small amounts in many foods and is a normal constituent of the blood and tissues. It is only when larger amounts are continuously ingested or inhaled by the lungs that the metal accumulates in the body and gives rise to poisoning. There seems no reason to believe that lead is absorbed from the unbroken skin, but it may be absorbed through an abrasion or carried to the mouth and swallowed with the food. Lead is apparently **Absorbed** more rapidly than most of the metals except mercury, and remains lodged in the tissues a long time, the excretion taking place only very slowly. It is found in most organs and tissues in cases of poisoning, particularly in the bones, liver and kidney. In the blood, 90 per cent is said to be carried in the red cells. Lead has also been found in the cerebrospinal fluid in cases of poisoning. It is **Excreted** in the urine, the bile, the secretion of the intestinal epithelium, in the milk and saliva, and in traces in the perspiration. The average ratio of excretion of lead between the urine and feces in cases of chronic poisoning is 1:2.5 (Aub).

Chronic Lead Poisoning is the commonest of all forms of metallic poisoning and, at the same time one of the most insidious. It is always accidental and, although it is most common in workers in lead, may occur in persons who are not apparently liable to come in contact with the metal. Some people are more susceptible to lead than others and persons who have suffered from the early symptoms may recover and prove resistant to the further action of the metal. Anemia and weakness from any cause are generally believed to predispose to the disease; women and children are more liable to it than men, and alcoholism and previous lead intoxication increase the tendency to the attack. Relapses are very common, and may occur years after the first symptoms, even though there has been no further exposure in the interval. Lead smelters and refiners, workers in white lead factories, painters, plumbers, electricians, and typesetters are liable to lead poisoning from continually handling the metal; but other trades are not exempt from it, and sometimes the channels by which it gains entrance to the body are very obscure. Trades which have recently yielded a considerable number of cases are pottery, from the use of a lead glaze, and coach-painting from the rubbing down of the layers of paint. Some of the more common industries in which lead poisoning is found are among the makers of lead wire, sheet lead, pipe, picture frames, car and can seals, stoppers for bottles and basins and other industries involving the handling of solid or molten metallic lead. The making of storage batteries involves the use of lead oxide and from the great growth of this industry it is proving an important source of cases of chronic poisoning. The painters' trade still furnishes a high incidence of poisoning and the use of the "spray gun" is likely to cause plumbism unless a specially constructed mask is worn to hold back the droplets containing minute quantities of lead. Formerly a common source of poisoning was wine and cider to which lead had been added to reduce the acidity. Cases of poisoning have been recorded from the use of lead preparations as

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abortifacients. Poisoning has also resulted from the use of acid beverages, and even drinking water which has been exposed to lead piping, or lead containers. Children have been poisoned by eating lead paints on furniture. The use of battery casings as fuel has led to "epidemics" of lead poisoning. Chronic lead poisoning has been induced experimentally in animals by the inhalation of lead carbonate dust and in birds by passing lead shot into the crop. Young animals are much more susceptible to lead poisoning than older animals.

The majority of cases of industrial poisoning have resulted from the inhalation of fumes or dust containing lead. It has been shown that in addition to the lead which may be absorbed by way of the stomach, the metal may also reach the circulation through the mucous membrane of the respiratory tract. With the recent emphasis on industrial health, preventive measures have been adopted against lead poisoning and its incidence has been greatly reduced.

The **Symptoms** of chronic lead poisoning vary greatly in different cases. Although often presenting a clinical picture which is pathognomonic, the disorder in its early stages may be difficult to diagnose. At this stage the patient may show signs of irritability and nervousness. There is often a pallor of the skin which is out of proportion to the anemia which may be slight. In the advanced form of lead poisoning, however, certain well defined signs and symptoms become evident.

The **Mouth, Stomach, and Digestion** very often give early indications of lead poisoning. The patient complains of loss of appetite, nausea, constipation, wasting, a metallic taste and fetid breath, and a blue-black line is seen along the margin of the gums close to where the teeth enter. This "lead line" is due to the precipitation of lead sulfide by the hydrogen sulfide arising from septic processes in the teeth and gums; it is often absent if the teeth and mouth are kept clean and healthy, and its presence does not indicate lead poisoning, but only contact with lead. The lead is not deposited on the surface but in the subepithelial tissue, as it cannot be removed by rubbing. The metallic taste seems due to the excretion of lead in the saliva, and the loss of appetite may arise from the same cause. These symptoms may be produced in animals also.

Another early symptom is **Anemia**, which, however, is usually not profound except in severe cases of poisoning. This anemia is due to the toxic effect of lead on the bone marrow as well as to an abnormal destruction of the red cells of the blood. The white corpuscles are increased in many cases but not in all. The anemia is sometimes accompanied by jaundice, a highly pigmented urine and other symptoms which usually follow the liberation of large quantities of hemoglobin from the breaking up of red cells. The red blood cells often contain granules staining with basophile dyes (stipple cells) and indicating incomplete disappearance of the nucleus; this change may present itself before any other symptom and is an important diagnostic sign of lead poisoning; it may, however, occur also in other forms of anemia. Lead is believed to alter the surface of the red blood cells, causing them to shrink and rendering them less elastic than normal and more brittle, as a result of which they break

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up easily, explaining the anemia. The loss is partially compensated for by new young erythrocytes, but these are affected by the lead also, so that the basophilic material is clumped together, giving the stippled appearance.

The **Lead Content** of the **Blood** in plumbism varies from 0.1 to 0.6 mg. per 100 cc. compared to 0.031 mg. in normal individuals. The concentration of lead in the urine of normal individuals varies from 0.03 to 0.05 mg. per liter while in individuals exposed to lead, the urinary content may exceed 0.3 mg. per liter. Likewise the fecal excretion of lead which is normally less than 0.5 mg. may be increased over ten fold in those exposed to lead. The lead content of the excreta thus reflects the degree of exposure to lead. Occupational exposure is considered safe if it does not lead to a lead output exceeding 0.6 mg. per day in the feces or a urinary concentration in excess of 0.1 mg. per liter (Kehoe).

Abortion is very often met with in lead poisoning, and in women employed in lead-works who do not show any marked symptoms of disease. In animal experiments it is found that the offsprings of a male suffering from lead poisoning are undersized, delicate and of slow growth; in most cases the spermatogenesis in the parent is not affected but some become sterile and the germinal epithelium atrophies.

One of the commonest symptoms is **Lead Colic**, painters' colic, colica saturnina or colica pictonum. This generally sets in suddenly, and is accompanied in most cases by obstinate constipation, in a very small proportion by diarrhea. Paroxysms of the most acute agony are followed by intervals of comparative freedom from pain, but in these intervals some tenderness of the abdomen may be complained of, while during the attack pressure generally relieves the pain. The colic lasts for several days, or a week, and then disappears, but is liable to return at intervals. The abdomen is generally hollow, retracted and hard, and during the acute spasms the patient often gains some relief by lying on his face with the fists pressed against the umbilical region, to which the pain is usually referred. Vomiting is frequently present, the pulse is slow and very hard, especially during the acute crises, while the respiration may be accelerated. The urine is scanty and often contains hematoporphyrin.

The cause of lead colic is evidently spasm of the intestine, but it is uncertain whether it arises from action on the muscle or on the ganglionic plexus. It can be induced in animals, and is relieved by atropine. The blood-pressure is raised in man, not only during the spasms, but also in the intervals. This contraction of the vessels, like the slowing of the pulse, is often said to be reflex from the pain, but this seems to be disproved by the fact that it remains during the intervals. Some writers have therefore regarded the colic and its attendant symptoms as due to a vascular spasm, and have supported this by showing that nitrite of amyl, which dilates the vessels, also relieves the colic.

Another common result of chronic lead poisoning is **Paralysis**, lead or painters' palsy, paralysis saturnina, which is most commonly limited to the extensors of the forearm and sometimes the foot, giving rise to

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"wrist drop" (Fig. 5) and "foot drop" respectively. It is bilateral in many cases, but sometimes involves only one arm. The affection generally begins in the middle and ring fingers, which cannot be extended, then spreads to the index and little finger, and afterward to the thumb and wrist. The fingers remain flexed and later the wrist is similarly affected. The muscles affected atrophy rapidly, and in old cases contracture of the flexor muscles sets in, when the limb becomes immovable and has a characteristic claw-like appearance. More rarely other regions are affected, such as the laryngeal muscles, the external

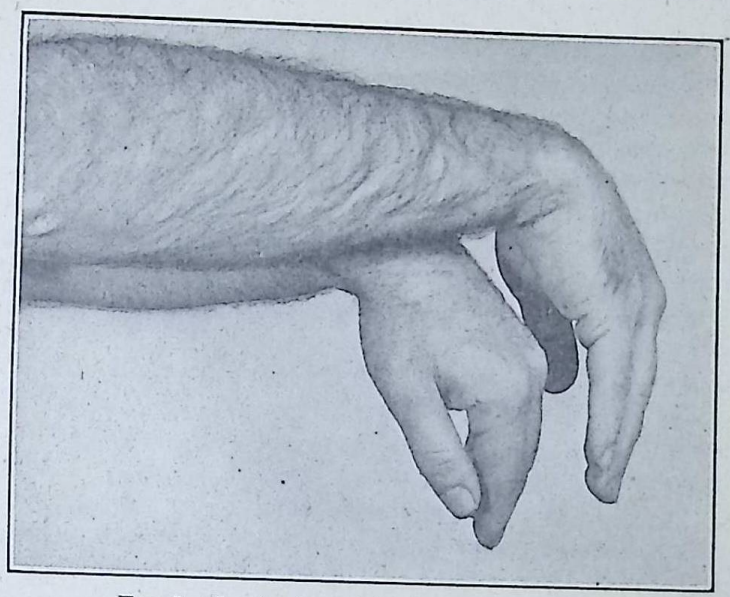

FIG. 5.—Lead palsy of the forearm extensors.

rectus of the eye, or the muscles of the leg. In animals several observers have succeeded in inducing paralysis of the hind limbs, and the legs are said to be affected very often in young children. When paralysis is complete, the reaction of degeneration is given by the muscles on electric stimulation, and even muscles which are not completely paralyzed are said to give it in some cases. The cause of lead palsy is peripheral neuritis and degeneration of the nerves, which sometimes involves secondarily the cells of the anterior horn of the spinal cord. Not infrequently the onset of palsy is very sudden, and this has been ascribed to small hemorrhages in the nerve trunk. Peripheral neuritis and paralysis have been elicited repeatedly in animals. According to Edinger's view, the nerves of those muscles are selected by lead, which are least developed in proportion to the work they have to perform. Aub and his co-workers believe the primary lesion is in the muscle. The afferent fibers are also involved in the action, as is shown by local **Anesthesia**, which is generally sudden in its onset, but may be preceded by numbness or tickling of the skin, and generally lasts only one or two weeks when sensation returns again to the part.

Lead **Arthralgia**, which arises from the same action on the peripheral nerves, consists in sharp lancinating or boring pains around the joints,

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the intensity of the pain being comparable only to that of lead colic. It sets in suddenly, usually in the night, and generally disappears as suddenly.

Lead **Amblyopia**, or blindness, is one of the rarer affections. The sight may be lost completely, or may only be dim, and the onset may be sudden or gradual. It arises from neuritis of the optic nerve and degeneration of the retinal nerve cells, or in some cases may be the result of the changes in the kidney occasioning albuminuric retinitis or effusion into the optic sheath. In early cases of neuritis, the disease can generally be arrested and even complete restitution may take place, but if it is neglected, optic atrophy follows.

Under saturnine **Encephalopathia**, a number of disorders of the brain are classed together. These cerebral symptoms sometimes appear suddenly, while in other cases they are heralded by violent headache, giddiness and sleeplessness, or by amblyopia, deafness, great depression, stupor, weakness, and tremor. Later, sudden mania and delirium, with convulsions resembling chorea or epilepsy, hallucinations and illusions indistinguishable from those of alcoholic delirium, sudden apoplectic paralysis, ataxia, partial analgesia, hyperesthesia, or coma may occur separately or in succession.

In animals cerebral symptoms are readily induced by lead in chronic poisoning. Chorea, tremors and general convulsions have been caused in this way in dogs.

The encephalopathia is obviously of cerebral origin, and at autopsy atrophy of parts of the cerebrum, or hemorrhages and very frequently disease of the brain vessels have been met with. In other cases of undoubted encephalopathia in man, no such lesions have been observed; and many of the symptoms are obviously not due to these gross lesions, for the suddenness of their onset and of the recovery precludes any such explanation, and shows that lead has also a direct action on the brain cells.

Another organ acted on by lead especially in prolonged poisoning is the **Kidney**, which is often found to present a typical red granular nephritis. During life the urine presents the ordinary appearances of this disease, being copious in amount and of low specific gravity, and containing comparatively small quantities of albumin or casts. In some cases in man, the kidney has presented a mixture of parenchymatous and interstitial disease, while in animals the parenchyma alone is affected, perhaps because the experiments have not lasted long enough. The disease of the kidney from lead poisoning, as from other sources, may cause dropsy, uremia and amblyopia, but the brain and eye may be affected in cases in which there is no nephritis.

Renal damage is also probably responsible for the hypertension which is seen in some cases of chronic lead poisoning. An elevation in blood-pressure has been induced in animals to which small amounts of lead have been administered over long periods.

Lead poisoning runs no definite course. As a general rule the anemia, wasting, constipation and weakness appear early, and then colic may

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follow, or paralysis, or arthralgia. Nephritis, encephalopathia, anesthesia, and gout are rarer, and as a rule occur only in very prolonged poisoning. In children and in those poisoned by tetraethyl lead, encephalopathy may be the first symptom noted.

The diversity of the forms of chronic lead poisoning is due to the various organs and systems of the body which may be involved. The central nervous system is certainly acted on, both in its higher and lower divisions. The lead line, metallic taste and nausea, and perhaps the constipation, would seem to be connected with the excretion of the metal along the alimentary canal, while the renal action is probably of the same nature as that inducing periarteritis in the brain and in the lungs under some conditions. Some authorities are disposed to regard the action on the vessels as the fundamental feature in lead poisoning which leads to all the other symptoms; thus, the colic is said to be a vascular spasm and the encephalopathia and palsy to arise from capillary hemorrhages. The anemia indicates an action on the red cells of the blood, and the gout, some disturbance of the general nutrition.

In chronic poisoning lead is found in the bones, in which it is deposited in the form of the insoluble tertiary phosphate. The lead thus deposited is without effect on the organism but when released from the bones in sufficient amount to give a toxic blood level induces the symptoms of lead intoxication.

Lead acts upon so many tissues that it might be expected to have some distinctive action upon the simpler organisms, but, as a matter of fact, it seems less poisonous to them than most other heavy metals.

Organic Lead combinations have been investigated in the hope that their action might throw light upon that of the metal. *Triethyl lead* ($Pb_2(C_2H_5)_6$) has been examined in the hope that it might be decomposed in the tissues to simpler lead compounds, but the effects seem to arise from the unaltered molecule, and cannot be brought into analogy with those of the metal.

Lead tetraethyl, $Pb(C_2H_5)_4$, is of considerable importance from its industrial use as an "anti-knock" constituent of gasoline. It is a clear heavy oily liquid, insoluble in water, soluble in alcohol and oils, and somewhat volatile at ordinary temperatures. Poisoning in man occurs mainly by absorption from the skin and lungs, and the chief symptoms induced are insomnia, nausea, pallor, low blood-pressure and temperature, loss of weight, tremor and sometimes delirium or mania. In acute poisoning, symptoms may come on in a few hours. Colic is frequent, but neuritis and the lead line are rare and the stippling of the red cells does not appear until very late.

Therapeutic Uses.—Lead is used in therapeutics only for its astringent action, but in view of its potential toxicity and the availability of equally effective substitutes, it may well be discarded from medical use. The intravenous injection of colloidal lead has been suggested in the treatment of cancer but this form of therapy has not been successful.

Prevention of Chronic Poisoning.—The most important factor in the prevention of chronic poisoning is the avoidance of dust, as absorption

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of lead from the respiratory tract is quite rapid. Wet processes of manufacture should be substituted for dry wherever possible and suction draft should also be employed to draw the dust from the workers. Workers should not wear the same clothes when at work as at their homes. Separate rooms should be provided for eating purposes and the hands should be carefully washed before handling food. Frequent careful medical examinations, including an examination of the blood and the determination of the lead content of the urine, should be made of all persons exposed to lead to determine their fitness for the work and to detect early signs of poisoning.

Treatment of Poisoning.—In the treatment of lead poisoning it is desired to use measures which favor the deposition of calcium (and incidentally of lead) salts in the bones, thus removing the lead from the circulation and depositing it in an inert form in the skeleton. For this purpose a diet high in calcium and phosphorus and alkalinizing salts (sodium lactate or citrate) should be administered. Milk is a good source of calcium and phosphorus and should be taken in large amounts (2 liters or more daily). Calcium lactate may be given in doses of 4 grams three times daily. After the symptoms have subsided it may become desirable to delead the patient. Mobilization of lead from the bones is brought about by the administration of a low calcium, high phosphate diet combined with an acid producing salt such as ammonium chloride. Other drugs which have been used in increasing the rate of excretion of lead are ascorbic acid, potassium iodide, sodium bicarbonate, magnesium sulfate, and parathyroid extract. With any method of treatment care must be taken not to convert a quiescent state into an acute one by the too rapid mobilization of lead. There is indeed some question, as to the advisability of using any measure to delead the patient, for ultimately if removed from the source of lead, the accumulated metal will be gradually excreted. Any condition inducing acidosis may, however, precipitate an attack of plumbism as long as large amounts of lead are still present in the bones.

In colic, morphine or opium is often necessary to allay the pain. Belladonna or atropine is used less frequently, and nitrite of amyl is said to be efficient for a short time. The intravenous injection of 15 cc. of 5 per cent calcium chloride also effectively relieves the colic. In the intervals between the paroxysms, a saline cathartic is often indicated to relieve the constipation, or if the vomiting prevents this, a large enema may be thrown into the bowel. Lumbar puncture is also advocated in encephalopathy.

In arthralgia, the pain may necessitate the giving of opiates. In anesthesia and encephalopathy, the treatment is expectant and symptomatic; for instance, in mania, or violent delirium, the hypnotics may be necessary.

In paralysis, strychnine may be used along with the general treatment, but the chief reliance is to be placed on the electrical stimulation of the paralyzed muscles, first with the galvanic current, and, as recovery sets in, with the induction coil. Massage of the muscles is also of benefit.

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PREPARATIONS

U. S. P.

PLUMBI ACETAS, lead acetate, sugar of lead ($Pb(C_2H_3O_2)_2.3H_2O$), forms colorless crystals, with a sweetish, astringent, afterward metallic taste, very soluble in water, less so in alcohol.

B. P.

EMPLASTRUM PLUMBI, lead plaster, diachylon plaster.
LIQUOR PLUMBI SUBACETATIS DILUTUS, contains about 0.25 per cent of lead.
LIQUOR PLUMBI SUBACETATIS FORTIS, contains about 20 per cent of lead.
PLUMBI ACETAS, 0.03 to 0.12 gram.
PLUMBI MONOXIDUM, orange scales or powder, almost insoluble in water.
SUPPOSITORIUM PLUMBI CUM OPIO, each contains about 0.2 gram of lead acetate and about 0.06 gram of opium.

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VI. SILVER

The only inorganic salt of silver used at all extensively in medicine is the nitrate, which is caustic, astringent, and disinfectant. Added to solutions of proteins, it forms a heavy precipitate, which is at first white in color, but turns darker in the light as the silver is reduced.

Symptoms.—In dilute solution silver is a slight irritant to the skin, and causes redness and itching only, but more concentrated solutions blister, and the solid nitrate of silver causes an eschar, which is at first white, but later turns black from the reduction of the silver in light. On the mucous membranes, dilute solutions act as astringents, but concentrated cause irritation and corrosion. The caustic action of silver does not extend so deeply as that of some other metals, such as mercury, because the penetration of the metal is limited by the formation of the insoluble chloride. On the other hand, the silver salts are more irritant than those of lead.

The astringent action is due to the formation of a protective layer of coagulated albumin. If irritation is induced, the vessels are dilated, and

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there is no evidence that they are ever contracted in the practical use of silver.

In acute silver poisoning from the ingestion of silver nitrate, the symptoms are those of severe gastro-intestinal irritation and corrosion. Burning pain is felt in the throat and abdomen, and is followed by nausea and vomiting and often by purging. The mouth is covered with a grayish-white membrane, which turns darker after a time, but this is absent if the poison is swallowed in the solid form, as has happened sometimes. The corrosion of the stomach and intestine causes collapse, with weak pulse, shallow respiration and pinched features and this may be followed by coma, convulsions, and death. The throat, stomach and intestine presented the ordinary appearances of acute corrosive poisoning in one case in which an autopsy was performed.

Action.—The symptoms of acute poisoning are due to the local action, and present no features suggesting that silver is absorbed and causes general poisoning. The action of silver after absorption has, however, been investigated in animals poisoned by subcutaneous or intravenous injection. The nitrate, owing to its coagulating properties, is unsuitable for this purpose, and the hyposulfite of sodium and silver, or a solution of the albuminate has therefore been used. In mammals the central nervous system is the chief seat of action, especially the medulla oblongata, which seems to be stimulated at first, for the blood-pressure rises and the pulse is somewhat slow, owing to increased activity of the vasomotor and vagus centers. Later the blood-pressure falls and the respiration becomes slow and labored, and eventually ceases from paralysis of the center. The diaphragm, and eventually the other striated muscles are paralyzed soon afterwards. The heart is comparatively little affected and often continues to beat some time after the respiration has stopped. In less acute poisoning, when the animal survives the injection for several hours or days, a marked increase in the bronchial secretion, culminating in edema of the lungs, has been noted; no satisfactory explanation of this has been advanced, but it does not seem due to cardiac inefficiency. Congestion and ecchymoses are found in the stomach and intestine, and some authors mention ulceration of these mucous membranes. Cohnstein found that small quantities of silver salts injected intravenously cause some increase in the urine for a time, but that larger quantities are followed by albuminuria.

In cold-blooded animals and in invertebrates, silver preparations are said to cause violent convulsions resembling those of strychnine and followed by general paralysis.

The general action of silver is thus apparently directed first of all against the medulla oblongata, the rest of the central nervous system being affected to a less extent. The mucous membrane of the stomach and intestine is acted on, as by most heavy metals, and the kidney is also liable to irritation. Edema of the lungs occurs frequently.

Chronic Poisoning.—There is no evidence that in acute poisoning in man any considerable amount of the metal is absorbed from the stomach and intestine. When silver is given for prolonged periods, however, some is absorbed, although probably only a minute fraction of that actually swallowed. None of it is found in the epithelium of the stomach and intestine, and some of it may circulate in the blood in a soluble form for a short time. But the greater proportion is very soon thrown down in the form of minute granules, which are found chiefly in the connective tissues of the body, and when present in quantity, give a dark color to the skin and mucous membranes. This pigmentation (Argyria) was

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much commoner formerly, when the nitrate was used in the treatment of epilepsy. It is occasionally observed in patients who have used "nose drops" or gargles containing silver over a long period. It has also occurred in the makers of artificial pearls, who use silver as a pigment. Local argyria is sometimes met with from the prolonged application of silver nitrate to the eye or throat, when it tints the eyelids and mouth, and from working with silver, when the hands are permanently blackened from the granules being forced into the skin.

The deposit of the silver in the skin gives it a darker color, varying from light gray in mild cases to a darker slate shade after more prolonged use. It is generally distributed all over the body, but in some cases has been especially marked in the face. The first evidence of discoloration is in the gums, where it causes a dark, slate-colored line somewhat resembling the lead line and in the scleræ which become light blue or gray In the skin it is found in the corium, not in the epidermis. The deposit and the dark color extend throughout the alimentary canal and the respiratory passages, the granules occurring in the connective tissue, particularly in the intestinal villi, and not in the epithelium. The glomeruli of the kidneys, the connective tissue of the liver and spleen, the choroid plexus, the tunica intima of the aorta, the serous membranes, and the mesenteric lymph glands contain more of the deposit than other organs. The pigmentation is not accompanied by any other symptoms of importance, and the victims may live to old age without suffering from the chronic poisoning in any way, except from the annoyance induced by the change in color.

Argyria is difficult to eradicate, although many attempts have been made to remove it. Iodide has been tried, for the most part without effect, and blistering is equally valueless, as the pigment lies deeper than the epidermis. The intradermal injection of sodium thiosulfate and potassium ferrocyanide has given the best results (Stillians).

Argyria has been induced in animals by prolonged treatment with small doses of silver salts, though here the pigment is not found in the skin, but in the connective tissue of the internal organs.

In man it seems likely that most of the silver passes through the alimentary canal unabsorbed and that the small proportion taken up by the tissues is precipitated and remains embedded in them indefinitely, for the pigmentation remains unchanging in its depth, and there is therefore no reason to suppose that any of the silver is eliminated. The silver content of the body increases with age due to the constant accumulation of small amounts through the years (Gaul and Staud).

In animals, however, some of the silver injected hypodermically or intravenously is excreted by the epithelium of the alimentary canal. None appears in the urine. In the frog, silver injected hypodermically is all excreted by the epithelium of the tongue, is swallowed, and passes out in the feces. No other poison is known to be eliminated by this channel.

Silver nitrate is a powerful disinfectant, partly from its action in coagulating the proteins of the microörganisms, partly from the specific effects of the metal.

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Therapeutic Uses.—The ancient use of silver oxide in the treatment of various nervous diseases dates from the Arabs, and originated from the astrological medicine of that period, which taught that nervous diseases were especially affected by the phases of the moon, which was associated with silver in their system (hence lunar caustic, lunacy). This use of silver often gave rise to argyria without benefiting the patient.

Externally silver nitrate is employed very extensively, the sticks of lunar *caustic* being used to destroy warts and other small skin growths, to arrest capillary hemorrhage, to destroy the false membranes of diphtheria and for other similar purposes. A solution of 2 to 5 per cent may also be applied to cauterize chancres and indolent *ulcers*, and weaker solutions are employed for their astringent-antiseptic action for fissures of the lips, impetigo, etc. A solution of common salt may be used to wash the part to remove the excess of silver as insoluble chloride.

Silver has a wide use for application to mucous membranes, as it is not only a good astringent but a powerful antiseptic, being especially valuable for gonorrheal infections, *e. g.*, of the eye or urethra. For ophthalmia it is extremely valuable. For the prevention of *ophthalmia neonatorum* a routine treatment is to wash the eyes of the infant with a solution of silver nitrate. Credé's method, which was once the accepted practice, consisted of the instillation of 1 drop of a 2 per cent solution of silver nitrate into each eye after the conjunctiva and lids had been carefully cleaned. This is, however, not without danger and many cases are on record where this procedure had resulted in permanent corneal opacity with gross diminution in vision. It is stated to be as efficient and much safer to employ a solution of one of the organic silver compounds. Silver is also used for other types of conjunctivitis and for trachoma.

In gonorrheal urethritis and proctitis silver is widely used, in the form of weak solutions of the nitrate (1 in 200 to 500) or of the colloidal silver derivatives (*cf.* p. 788). For pyelitis, lavage of the renal pelvis, through a ureteral catheter, has been practiced, using 1 per cent of silver nitrate or stronger solutions of protein or colloid compounds. Solutions are used in a similar way for cystitis and have been injected into the rectum for chronic dysentery. Generally for more sensitive mucous membranes, such as the eye and urethra, the milder protein compounds are tending to replace silver nitrate itself, as they achieve the same effect with less irritation. These compounds are described on page 789.

For *silver arsphenamine*, see p. 183.

In cases of **poisoning** with silver nitrate, eggs, milk and, above all, common salt solution are indicated to form insoluble compounds.

Preparations

Argenti Nitras (U. S. P., B. P.) ($AgNO_3$), colorless crystals which become gray or grayish-black on exposure to light in the presence of organic matter, with a bitter, caustic, strongly metallic taste, very soluble in water, less so in alcohol. Dose, B. P., 0.008 to 0.016 gram.

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ARGENTI NITRAS INDURATUS (U. S. P., B. P.), moulded nitrate of silver, lunar caustic—a white, hard solid, generally cast in the form of pencils, and containing about 95 per cent of silver nitrate.

The silver preparations ought to be kept in dark amber-colored bottles, in order to prevent their being reduced by light, and ought not to be prescribed with organic matter, which rapidly reduces them.

The protein compounds of silver are described under antiseptics (p. 788).

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VII. MERCURY

Mercury, one of the most powerful inorganic poisons, has been used in medicine for a long time and in a large variety of forms. Some differences are observed in the action of these, but all of them induce the same general results, the differences existing only in their local effects, and being due to the salts differing in solubility and dissociability. A soluble salt, such as the bichloride, comes into more intimate contact with the tissues, and therefore acts more powerfully locally and is also absorbed more rapidly and in larger amount than calomel, which is entirely insoluble in water. The organic mercury compounds do not dissociate to give mercuric ions and hence are neither corrosive nor toxic on immediate application to the tissues. However, when sufficient mercury in the form of calomel is absorbed into the tissues, the general effects are the same as if an equal quantity had been taken up as bichloride.

The corrosive action of the soluble mercury salts is doubtless due in part to their precipitation of the proteins, but in addition to this there is a specific toxic action on all living cells. Less of the insoluble preparations are absorbed merely because they come into less intimate contact with the tissues than the soluble and dissociable bichloride; but even the metal may be oxidized and absorbed when it is applied to the living surfaces or injected into the blood in a state of fine division. Thus the inhalation of mercury vapor by the lungs leads to general poisoning, often of a very malignant type, and mercury rubbed into very fine globules, and applied in ointment to the skin, passes into the gland ducts and along the roots of the hairs, and is absorbed into the tissues, in which it causes the typical mercurial effects.

Symptoms.—Acute Mercurial Poisoning occurs only from the use of soluble preparations, and in particular from the bichloride of mercury, or corrosive sublimate. Many cases have arisen from this poison being swallowed accidentally or with suicidal intent, or from its use as a disinfectant wash for large cavities. Fatal cases have occurred from the use of mercury solutions as a vaginal douche. When corrosive sublimate is swallowed in poisonous quantity, the patient complains at

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once of the harsh metallic taste, which is followed by burning pain in the mouth, throat, and stomach. Nausea and vomiting set in very soon, and the vomited matter may contain shreds of mucous membrane and blood. Diarrhea and violent tenesmus, with watery or bloody stools, often containing shreds of membrane, may be among the early symptoms, or may only occur after twenty-four hours. These symptoms from the alimentary canal are accompanied by collapse, with a small, thready, sometimes irregular, pulse; shallow, irregular, rapid respirations; cold, clammy skin; pinched features, and sunken eyes. The temperature is often subnormal, but sometimes fever is observed, although this is attributed by many to concurrent disease. The consciousness is usually unaffected, but in some cases somnolence, giddiness, or more rarely anxiety and restlessness have been observed. The urine is much diminished and complete anuria often occurs in a few hours. If the urine is not completely suppressed, it generally contains albumin, renal epithelium, casts and more rarely sugar. Death may occur within an hour from shock, but more frequently the patient survives several days or even one or two weeks, the symptoms of intestinal corrosion and of renal irritation continuing, until he finally sinks from exhaustion. Complete suppression of urine may exist for several days before death. Gangrenous colitis may occur, usually in six to twelve days. Corrosive sublimate has induced fatal poisoning in doses of 0.2 gram or even less, but other cases have recovered from much larger doses depending upon the rapidity of vomiting and the degree of absorption. If vomiting does not occur within ten minutes after swallowing 1 gram, the prospect for recovery is poor.

When acute poisoning occurs from the absorption of corrosive sublimate from wounds, the symptoms of corrosion of the mouth and stomach are absent at first, but the dysenteric symptoms and the renal inflammation are produced in the same way as when the poison is swallowed. Here again the patient may die within a few hours, but more frequently survives for several days, and in the latter case the symptoms toward the end partake of the character of chronic poisoning. In particular, salivation and stomatitis set in in the course of a few days. These also occur when the poison is swallowed, although they are more liable to be overlooked, from the cauterization produced in the mouth by the local action.

Chronic Poisoning.—A much more frequently observed form of poisoning is that induced by the prolonged medicinal use of mercury. It may arise from any of the preparations, and from any form of application, although some methods of administration are credited with being less liable to induce it than others. Thus inunction with mercurial ointment and the use of calomel internally are both more liable to cause the severer forms of stomatitis than is corrosive sublimate. A single hypodermic injection of an insoluble preparation may induce it in susceptible persons, because the mercury is only slowly absorbed, and passes into the tissues as gradually as if it were given by the mouth regularly for several days. Thus chronic poisoning, or **Mercurialism**, is due not to the local action, but to the effects of the drug after absorp-

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tion. It may follow the abuse of mercury in any case, but some individuals exhibit a special susceptibility from some unknown cause. Formerly it was believed that the earlier symptoms of mercurial poisoning had to be induced in the cure of syphilis, but in modern therapeutics every effort is made to avoid them. The first symptoms generally arise from the *mouth and throat*, the patient complaining of a metallic taste, and of a feeling of numbness or soreness of the tongue and gums. The breath has an unpleasant fetid odor, the tongue is swollen and thickly coated, the gums are soft, swollen and often of a dark bluish-red or gray color and the flow of saliva is augmented. If the medication be continued, as was often done formerly, ulcers appear on the gums and on the sides of the tongue where it comes in contact with the teeth, especially if these are carious, and on the mucous membrane of the cheeks; the salivation increases and irritates the lips and the skin where it is exposed to the secretion. If the administration of mercury be still persisted in, the teeth become loose and fall out, gangrene of the gums, lips and throat, and necrosis of part or even of the whole jaw may follow. The milder forms of stomatitis and salivation were observed very frequently when syphilis was treated with mercury, but since this form of therapy has been discarded, it is less often encountered. It may be avoided, to some extent at least, by scrupulous cleanliness of the mouth and teeth and by attention to carious teeth.

The *stomach and intestine* also suffer in chronic mercury poisoning. The patient often complains of loss of appetite, and occasionally of a feeling of weight and discomfort in the stomach, nausea and vomiting, general weakness and loss of flesh. Colic and diarrhea are frequently observed, or diarrhea and constipation may alternate. These symptoms are naturally more liable to occur from the administration of mercury by the mouth than by other channels, as here the action after absorption is reinforced by the direct local effects. Some *fever* is sometimes noted, but this is secondary to the affection of the mouth, bowel or skin, and is not directly attributable to the mercury.

Occasionally *skin eruptions* are seen when mercury is given by the mouth, but much more frequently when it is applied to the skin. In the latter case they are not limited to the point of application, although they often begin from it and spread over a large surface of the body. They vary greatly in form, consisting of small reddish spots, large red erythematous surfaces, urticaria, or eczema, each of these occurring alone or in succession, and being usually followed by desquamation. The eruption generally lasts only one to three weeks, but in some cases has not entirely disappeared until three months after its appearance, and in others has returned repeatedly afterwards. It is said to have been induced occasionally by a single dose of calomel.

The *urine* is often somewhat increased, but may be decreased afterwards, and it not infrequently contains albumin. Glycosuria is rare in man, but has been frequently observed in rabbits after prolonged treatment with mercury.

A general condition of *cachexia* may be induced by these disorders, and is marked by pallor, anemia, emaciation, weakness and restless-

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ness, with a tendency to fainting and disturbed sleep. The pulse is small, weak and quick, and the patient often complains of breathlessness.

Affections of the *central nervous system* are rarely induced now by the abuse of mercury in therapeutics, but still occur in the case of workers in mercury mines, in mirror, barometer, thermometer, and other manufactories, in which mercury is used and its fumes are inhaled by the workmen for prolonged periods. One of these affections is the mercurial *erethism*, a condition of abnormal irritability, timidity or shyness, accompanied by great muscular weakness, and sometimes developing into sleeplessness, delirium and transitory hallucinations. Another well-known form is the mercurial *tremor*, which affects the hands and arms first, later the legs, and sometimes extends over all the muscles of the body. Shooting pains along the nerves or in the joints are sometimes complained of, circumscribed areas of partial anesthesia, amblyopia, anosmia or deafness have been described, and in some cases localized paralysis of the muscles of the arm or leg has been induced.

The symptoms of mercurial poisoning, both acute and chronic, in animals, resemble those in man closely.

Action—Lower Forms of Life.—Mercury is destructive to living matter wherever it comes in contact with it in sufficient concentration. This poisonous action is naturally much more evident when soluble preparations are used than when the oxides or calomel are in question. Thus corrosive sublimate in a solution of one part in 50,000 destroys infusoria in some twenty minutes, and even one part in one million kills algæ in the course of a few days. Mercury in a dilution of 1 in 200,000 destroys spirochetes in the test-tube, but its spirocheticidal action *in vivo* is feeble. The therapeutic dose necessary to cure experimental syphilis in animals approaches the lethal. Mercury has little effect in malaria or trypanosomiasis, that is, it does not injure the organisms of these diseases in the same degree as it does that of syphilis. The bacteria are somewhat more resistant than these forms, but corrosive sublimate is said to delay the development of some of these in a solution of 1 part in 1,000,000, and the anthrax bacillus fails to grow in blood which contains 1 part in 8,000. A solution of 1 part in 1,000 is generally regarded as capable of disinfecting fluids completely in the course of a few hours. Much lower concentrations act as antiseptics if given sufficient time, time being necessary for the absorption and subsequent penetration of the metal. The presence of organic matter reduces the antiseptic action, so that mercury is not generally suitable for rapid disinfectant action, especially in the presence of excess of proteins. There is no doubt, however, that corrosive sublimate and the other soluble salts of mercury are among the most powerful antiseptics at present available. The insoluble preparations are less poisonous, owing to the difficulty in bringing them into intimate contact with the microbes.

In the **Higher Animals and in Man** the same destructive effects are induced by the mercury preparations. The corrosion of the mouth, throat and stomach when the bichloride is swallowed, has already

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been mentioned. When it is applied to the other mucous membranes, similar effects are obtained, and when it is injected hypodermically, even in dilute solution, it induces intense pain, swelling and inflammation, which is rarely followed by suppuration, but which may result in the formation of cicatrices.

When solutions of corrosive sublimate are applied to the skin, they cause a feeling of numbness very often; but when very strong solutions come in contact with tender parts of the skin, and in particular, when the salt itself is allowed to lie in contact with it for any length of time, deep corrosion, necrosis, and sloughing may follow. Even the insoluble preparations are liable to set up irritation when they are rubbed into the skin, especially if there is any preëxisting tendency to cutaneous eruption.

After absorption, mercury acts more especially on the alimentary tract and on the kidneys, although other organs are not exempt from its effects.

The Salivation and Stomatitis, which are so frequently seen under mercurial medication, are obviously not due to the local action of the drug on its way to the stomach, for they occur equally readily when it is applied by hypodermic injection or by inunction. The saliva is sometimes excreted in enormous amounts, many liters of it being poured out in the course of twenty-four hours. It contains mercury, and has therefore a metallic taste, and tends to irritate the lips and skin where it comes in contact with them. In extreme cases it leads to sleeplessness from its accumulating in the back of the throat and awakening the patient with a feeling of suffocation. The stomatitis is due to the excretion of mercury by the glands of the mouth and throat. The irritation caused by the metal leads to excoriations, and these to the formation of ulcers, particularly where microbes are present in large numbers, as around carious teeth. The necrosis of the jaws arises from these ulcers penetrating to the bone and setting up periostitis, for mercury in itself has no specific action on bone.

Mercury has less direct effect on the **Stomach,** though congestion and even small hemorrhages in cases of poisoning indicate that it is not entirely immune; the loss of appetite and malnutrition in chronic poisoning are ascribed to the presence of mercury in the saliva rather than to its affecting the gastric functions directly. In the **Intestine,** on the other hand, mercury is excreted in larger amount, and induces very distinct lesions. The parts affected are the cecum and colon, while the small intestine often escapes almost entirely. The action of mercury is evidenced by hyperemia, redness and swelling of the mucous membrane, which later develop into necrotic surfaces and ulcers along the folds; these lend it an appearance almost indistinguishable from that of chronic dysentery and may eventually end in perforation. The symptoms from the intestine are in accordance with the lesions, consisting of constant purging with very fluid, sometimes rice-water, stools, intense pain and tenesmus, blood and fragments of mucous membrane in the feces.

The **Purgative Action** of mercury may be described here. The soluble

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preparations and even those which are insoluble but are readily changed to soluble forms are too irritant to the stomach to be employed for their action on the bowel. But certain preparations pass through the stomach in an insoluble form and slowly unfold a mild irritant action on the bowel mucous membrane, and, rendering it more sensitive to the presence of its contents, increase the peristalsis in the same way as the vegetable purgatives. Calomel was formerly widely used as a purgative but has been replaced in large part by less toxic vegetable and synthetic cathartics. When calomel is administered a certain amount is absorbed into the tissues and is finally excreted in the urine, but in ordinary conditions this is small. But when calomel fails to evacuate the bowel, absorption may occur in larger measure, and severe poisoning may follow.

Small doses generally cause a soft stool without pain or straining, but after larger amounts there may be a considerable amount of fluid. In some people nausea and griping occur with calomel. Purgation usually takes place in eight to ten hours. The stools are often of a gray-green color and this has been attributed to the putrefaction of the bowel being lessened, so that the bile retains its original tint. But mercury acts when no bile reaches the intestine and the stools are of the same greenish color, so that it seems likely that this arises from the presence of some mixture of mercury sulphides in the stool.

Mercury is generally believed to act mostly on the small intestine, increasing the secretions and accelerating the passage of its contents.

The mercurial purges, and in particular calomel, have often been credited with increasing the secretion of the **Bile**, but they have not been found to have any effect on the secretion escaping from a biliary fistula. There is no experimental or clinical evidence that the liver is in any way affected directly by mercury. The "biliousness" which is so often relieved by calomel or blue pill, is due, not to the liver, but to disorder of the alimentary tract.

Mercury has no such powerful effect on the **Unorganized** ferments of digestion as it has upon the microbes, for though large amounts of the soluble preparations precipitate the pepsin in artificial digestion experiments, smaller quantities have little effect. Calomel has no action on the digestive ferments, but may retard the putrefaction in the intestine, and thus limit the decomposition of the food. Its antiseptic action is aided by the increased peristalsis which follows its use, and which removes the decomposing mass from the canal.

The **Kidney** is affected by mercury, a moderate dose of calomel inducing marked diuresis, particularly in cases in which there is a large accumulation of fluid in the body, as in dropsy from heart disease. When purging follows the administration of the mercurial, less diuretic effect is observed. In normal individuals and in animals the diuretic action is generally weaker; the kidney is affected directly and not through changes in the circulation.

In acute mercurial poisoning, when death does not follow in the course of a few hours, anuria is often observed with inflammation and necrosis of the epithelium of the tubules. The whole organ is congested

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and the glomeruli are in a state of acute inflammation, but the necrosed tubules are the most prominent feature. Very generally in the rabbit, less often in the dog and in man, these are filled with a deposit of phosphate of calcium, which is thrown out in the necrosed cells, and as these break up, passes into the tubules. It may be remarked in passing that several other poisons, such as bismuth, and aloin, occasionally induce this deposit of lime in the kidneys.

This renal necrosis occurs chiefly in corrosive sublimate poisoning, as the more slowly absorbed, insoluble preparations apparently do not often accumulate in sufficient quantity in the blood to induce such severe effects. At the same time, albumin or casts are often observed in the urine from the treatment of syphilitic patients with mercury in any form. The more marked the action on the intestine, the less destruction of the kidney is observed in cases of severe poisoning.

The action of mercury on the **Nervous System** is very obscure. In acute poisoning the intellect often remains clear to the end, and no symptoms pointing to any direct affection of the central nervous system are observed. In chronic poisoning, however, the higher centers are undoubtedly involved in the effects, as is shown by the erethism and occasional hallucinations. The tremor also is probably of cerebral origin though this is not yet certain, and the general muscular weakness is not due to the peripheral muscles and nerves being affected, but to the alterations in the centers. The paralysis sometimes observed in the arms or legs in workers in mercury, and the areas of partial anesthesia and the pains in joints probably arise from peripheral neuritis. In some cases, especially where the tremor is marked, the reflex excitability of the spinal cord has been found to be exaggerated but it is generally unaffected. The muscles do not seem to be acted on directly in either acute or chronic poisoning in man, and even when paralysis is developed, they maintain their irritability and do not atrophy.

Changes in the **Blood Corpuscles** have been observed under mercurial treatment in a number of instances, but these are not remarkable. Mercurial poisoning is sometimes accompanied by a leucocytosis which at times may involve principally an increase in the monocytes.

Mercury has no effect on the **Temperature** in itself, but when stomatitis or skin eruptions are developed, some fever generally accompanies them, while in collapse the temperature may fall several degrees below the normal.

Distribution.—After its prolonged use mercury is found in almost every organ of the body, but larger quantities are found in the kidney, liver, spleen, intestinal wall, skeletal muscle, bones and lungs. In cases of acute poisoning through absorption from the subcutaneous tissue or from wounded surfaces, the distribution is the same.

Mercury is **Eliminated** by almost all the excretory organs, but most largely by the intestine and kidney. It has been found in small quantities in the perspiration, milk, saliva, gastric juice and bile, and has been shown to pass to the fetus *in utero* through the placental circulation. The excretion in the urine begins within an hour when mercury is

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injected intravenously, but more slowly by the ordinary methods of administration; for example, after inunction, none may be found for twenty-four hours. The quantity eliminated daily rises slowly during the treatment and then falls gradually. The excretion is very slow and varies according to the method of administration; most of it is excreted within six days but after the usual methods of administration in syphilis mercury may be found in the urine for months and in some cases for years after the last dose. The administration of potassium iodide does not accelerate the elimination of mercury.

Therapeutic Uses.—For over three hundred years mercury was the principal drug used in the treatment of **Syphilis**, having been introduced for this purpose just before the beginning of the sixteenth century. With the discovery of arsphenamine, mercury retained its importance as a supplementary form of therapy used in conjunction with the organic arsenicals. However, because of its toxicity and inferior therapeutic value compared to bismuth, the latter metal has displaced mercury which is now only rarely used, except for prophylaxis of syphilis. For this purpose the ointment of mild mercurous chloride (calomel) is applied by inunction within an hour after exposure.

The mercurials were formerly largely used as occasional **Purgatives** for acute constipation, not so frequently in chronic constipation. In "biliousness" and in the diarrhea of putrefaction they had a high reputation, but their action here is not materially different from that of other purgatives. Very often a mercurial was taken at night and followed in the morning with a saline purgative such as Seidlitz powder. There is a marked variation in individual response to calomel; 30 mg. may produce as free purgation in one individual as 0.3 gram in another. It occasionally produces nausea and griping. In recent years the use of the mercurials as purgatives has been for the most part discontinued, these drugs being replaced by the less toxic vegetable and synthetic cathartics.

Calomel and other mercurials have long been known to be of value as **Diuretics** in cases of **Dropsy**. However, because of its cathartic effects and the uncertainty of its absorption from the intestine, calomel has been replaced as a diuretic by a group of organic mercurials. These presumably act by interfering with the reabsorption of water by the tubules. As with other mercury compounds, these compounds must be used with caution to prevent the cumulative toxic effects. They are particularly effective in edema due to congestive heart failure, but are also sometimes of value in nephrotic edema and ascites due to portal obstruction. The diuresis which follows the administration of the mercurial diuretics begins two to three hours after their administration and is over after twelve to twenty-four hours. The diuretic action is potentiated by the administration of acid-forming salts such as ammonium chloride which are best given at least forty-eight hours before the mercurial compounds are injected.

Mercurin, β-methoxy-γ-hydroxymercuri-propylamide of trimethyl cyclopentane dicarboxylic acid, is used as a diuretic in the form of its sodium salt combined with theophylline, one of the xanthine diuretics described on page 394. This combination of mercurin and theophylline,

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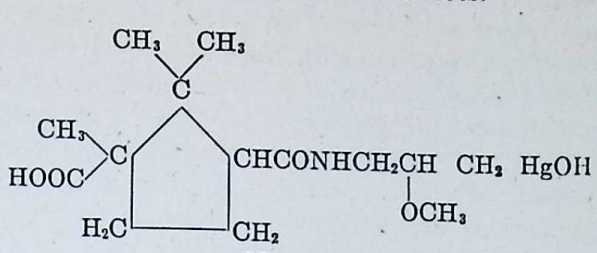
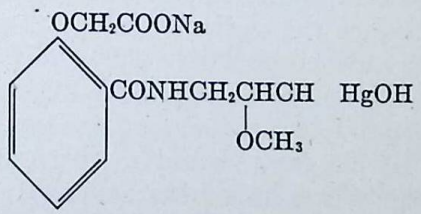
designated as mercurophylline, was introduced under the trade name, **Mercupurin**, and is available in 1 and 2 cc. ampules for intramuscular injection and in the form of enteric coated tablets.



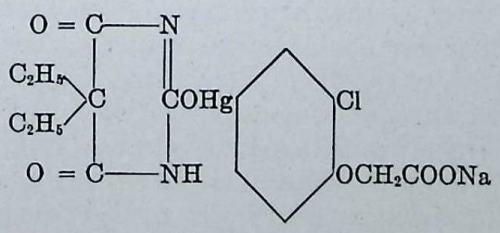
Mercurin

Mersalyl, a complex mercury derivative of salicylic acid was introduced under the trade name, **Salyrgan**, and is also used in combination with theophylline. This combination produces less local reaction on injection than mersalyl alone and is somewhat more effective. Mersalyl and theophylline is given by intramuscular or intravenous injection in doses of 1 or 2 cc. of a 10 per cent solution. Injections should not be given more frequently than every three or four days. An enteric coated tablet of the same drug (0.08 grams mersalyl and 0.04 gram theophylline coated with shellac) may be given daily for one or two weeks as an adjunct to parenteral medication, with rest periods of one or two weeks between courses of treatment.



Mersalyl

Merbaphen, another of the mercurial organic diuretics was introduced under the trade name, **Novasurol**, and is a double salt of sodium mercurichlorphenyl oxyacetate with barbital. It is administered intravenously or intramuscularly once or twice a week in doses of 0.5 to 2 cc. of a 10 per cent solution.



Merbaphen

Meralluride sodium, sold under the trade name, **mercuhydrin**, is the sodium salt of methoxyoximercuripropylsuccinylurea—theophylline. It is administered intramuscularly in doses of 1 to 2 cc.

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The use of mercury compounds as **Disinfectants** and **Antiseptics** is described under this heading on page 785.

Numerous ointments have been applied externally in the treatment of **Skin Diseases**, particularly those of a parasitic nature, such as itch, and in condylomata, ulcers, and skin diseases of syphilitic origin. These preparations combine a disinfectant with a more or less irritant action, and unlike carbolic acid and its allies, are equally powerful antiseptics in ointments and in water. Other external applications are the plasters and the black wash. Ointments containing calomel, corrosive sublimate and other preparations are sometimes prescribed, or calomel may be used as a dusting powder in syphilitic ulcers and as a prophylactic against infection. The mercury ointments are frequently applied to the eye, the milder ones as antiseptics and slight irritants, citrine ointment to destroy granulations.

The nitrate of mercury and its ointment (citrine) are sometimes used as caustics for application to the os uteri, condylomata, and elsewhere.

Mercury treatment is **Contraindicated**, or requires special caution in cases of profound cachexia, weakness or anemia. Where the digestion is weak and in cases of tuberculosis, it ought to be avoided if possible. In severe nephritis it is also to be used with caution, although it is beneficial in some cases, and although some authorities deny that it is injurious even when it has no diuretic action. In pregnancy mercury is not absolutely contraindicated, at any rate up to the sixth month. Later it is liable to injure the patient by its action on the digestion, and in some cases has induced abortion; the child may also suffer from mercurial poisoning. Mercurial ointments or dusting powders have to be used with care when iodides are being administered internally, as the iodide of mercury may be formed and may cause violent corrosion. Thus in the eye, severe effects have been induced by the application of calomel to the cornea while iodide of potassium was being given.

In cases of **Acute Corrosive Poisoning**, the indications are the evacuation of the stomach, preferably by the stomach tube. Tannic acid, or eggs, milk and other albuminous substances should be given to precipitate the metal and protect the mucous membrane.

Subsequent therapy consists principally in maintaining a normal composition of the body fluids and protecting the kidney from the toxic action of mercury. For this purpose large amounts of fluids should be administered to maintain a copious diuresis. Acidosis should be overcome by the use of alkalies. Blood transfusions are indicated if symptoms of shock appear. Colonic irrigation with isotonic saline is used to lessen the irritation of the colon resulting from the excretion of the metal through the gut. Rosenthal introduced the use of sodium formaldehyde sulfoxalate in acute mercury poisoning, the stomach being first washed out with a 5 per cent solution, and about 200 cc. left in the stomach. Immediately afterwards 10 grams of the drug dissolved in 100 to 200 cc. of distilled water is slowly injected intravenously, from twenty to thirty minutes being allowed for the injection. The antidotal action of sodium formaldehyde sulfoxylate depends on the reduction of

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soluble mercuric salts to the less soluble mercurous compounds by this drug. This treatment is only effective if it is given immediately after poisoning. Its value thereafter is questionable (Monte and Hull). Decapsulation of the kidney may be tried in cases of acute mercury poisoning which are not yielding to appropriate medical treatment but operative treatment is futile if the patient is moribund or if gangrenous colitis is present. (See also "Bal," p. 176)

Chronic Poisoning is treated symptomatically. Careful mouth and dental hygiene are indicated. Diarrhea may be treated with opium. Iodide of potassium and hot baths or sulfur baths are often advised in chronic poisoning with the view of accelerating the elimination of the metal, but careful estimations have shown that they have no such effect.

Preparations

U. S. P.

Hydrargyri Bichloridum, Corrosive Sublimate ($HgCl_2$), forms heavy, colorless crystals without odor, but possessing an acrid, metallic taste, soluble in 16 parts of cold water, in 2 parts of boiling water, in 3 parts of alcohol.

Hydrargyri Chloridum Mite, mild mercurous chloride, Calomel (Hg_2Cl_2), a heavy white powder, without odor or taste, insoluble in water, alcohol and ether. Dose, 0.12 gram; in powder or tablets, less suitably in pill form.

Hydrargyri Oxidum Flavum, yellow mercuric oxide, an orange-yellow, impalpable powder, almost insoluble in water.

Hydrargyri Salicylas, a white or yellowish powder, practically insoluble in water. Dose, 0.06 gram, in oil, intramuscularly.

Hydrargyri Salicylas, mercuric salicylate ($HgC_7H_4O_3$), a white or slightly yellow or slightly pink powder, insoluble in water. Dose, 0.06 gram, in oil, intramuscularly.

Hydrargyri Succinimidum, mercuric succinimide ($C_8H_8N_2O_4Hg$), a white crystalline powder, soluble in water. Dose, 0.015 gram, intramuscularly.

Hydrargyrum, mercury, quicksilver, a bright shining silver white metal, liquid at ordinary temperatures. Used in the preparation of Hydrargyrum Cum Creta and Unguentum Hydrargyri Forte and Mite.

Hydrargyrum Ammoniatum, mercuric ammonium chloride, white precipitate (NH_2HgCl), is formed by precipitating corrosive sublimate with ammonia, and is a white, amorphous powder, without odor and with an earthy, metallic taste, almost insoluble in water and alcohol.

Hydrargyrum Cum Creta, mercury with chalk, Gray Powder, is formed by rubbing up metallic mercury with chalk and honey until the mercury is divided into very fine globules, each encased in chalk. It forms a light-gray, somewhat damp powder, without odor and with a sweetish taste from the honey. The mercury (38 per cent) remains in the metallic state, very little oxide being formed. It is insoluble in water, alcohol and ether, and is always prescribed in powder form. Dose, 0.25 gram.

Injectio Hydrargyri Salicylatis, a sterile suspension of mercuric salicylate in oil. Dose, 0.1 gram intramuscularly.

Injectio Mercurophyllinæ, a sterile solution in water of the sodium salt of β-methoxy-γ-hydroxymercuri propylamide of trimethyl cyclopentane dicarboxylic acid and of theophylline. Dose, 0.14 gram intramuscularly.

Mersalyl ($C_{13}H_{16}HgNO_6Na$), a white crystalline powder, soluble in water. The double salt of mersalyl and theophylline is available as Injectio Mersalis et Theophyllinæ for intramuscular injection. Dose, 0.3 gram.

Oleatum Hydrargyri, oleate of mercury, has been used for the same purposes as mercury ointment, but is somewhat more irritant and possesses no compensating virtues. It contains 25 per cent of yellow mercuric oxide in oleic acid.

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TOXITABELLÆ HYDRARGYRI BICHLORIDI, MAGNÆ AND PARVÆ. The large tablets contain about 0.5 gram of $HgCl_2$, the small, 0.125 gram.

UNGUENTUM HYDRARGYRI AMMONIATI, a 5 per cent ointment of ammoniated mercury.

UNGUENTUM HYDRARGYRI FORTE, mercurial ointment, is formed by triturating metallic mercury with wool-fat and petrolatum until the globules are invisible when magnified 10 diameters. The ointment contains about 50 per cent of metallic mercury.

UNGUENTUM HYDRARGYRI MITE, BLUE OINTMENT, contains 33 per cent of mercury.

UNGUENTUM HYDRARGYRI OXIDI FLAVI, a 1 per cent ointment of yellow oxide of mercury.

B. P.

HYDRARGYRI IODIDUM RUBRUM. Dose, 0.002 to 0.004 gram.

HYDRARGYRI OXIDUM FLAVUM, yellow mercuric oxide, an orange-yellow amorphous powder, insoluble in water.

HYDRARGYRI OXYCYANIDUM, a white powder, soluble in about 18 parts of water. By intramuscular injection, 0.005 to 0.01 gram; by intravenous injection, 0.01 gram.

HYDRARGYRI PERCHLORIDUM, mercuric chloride, corrosive sublimate. Dose, 0.002 to 0.004 gram.

HYDRARGYRI SUBCHLORIDUM, calomel. Dose, 0.03 to 0.2 gram. By intramuscular injection, 0.03 to 0.06 gram.

HYDRARGYRUM AMMONIATUM, white precipitate, a white powder insoluble in water.

HYDRARGYRUM CUM CRETA, gray powder, 1 part of mercury with 2 of chalk. Dose, 0.06 to 0.3 gram.

HYDRARGYRUM OLEATUM, mercuric oleate, contains the equivalent of 20 per cent of mercuric oxide.

INJECTIO HYDRARGYRI, 10 per cent in wool-fat, olive or arachis oil, camphor and creosote. Dose, 0.3 to 0.6 mil. by intramuscular injection.

INJECTIO HYDRARGYRI SUBCHLORIDI, 5 per cent in wool-fat, olive oil, etc. By intramuscular injection. Dose, 0.6 to 1.2 mil.

LIQUOR ARSENI ET HYDRARGYRI IODIDI, Donovan's solution. Dose, 0.3 to 1 mil.

LIQUOR HYDRARGYRI PERCHLORIDI, 0.1 per cent in distilled water. Dose, 2 to 4 mil.

LOTIO HYDRARGYRI NIGRA, contains black mercurous oxide from interaction of calomel with calcium hydroxide. Used as a local remedy in syphilitic lesions.

MERSALYLUM. Mersalyl (Salyrgan) contains 39.6 per cent of mercury. It is very soluble in water. *Injectio mersalyli* (B. P.) is a 10 per cent solution. Dose, 0.5 to 2 mil. by intramuscular or intravenous injection.

OCULENTUM HYDRARGYRI OXIDI, 1 per cent.

PILULA HYDRARGYRI, blue pill, 33 per cent. Dose, 0.25 to 0.5 gram.

TABELLÆ HYDRARGYRI CUM CRETA, tablets of mercury with chalk. Dose, 0.06 to 0.3 gram.

TABELLÆ HYDRARGYRI SUBCHLORIDI, tablets of mercurous chloride. Dose, 0.03 to 0.2 gram.

UNGUENTUM HYDRARGYRI, blue ointment, 30 per cent.

UNGUENTUM HYDRARGYRI AMMONIATI, 2.5 per cent in simple ointment.

UNGUENTUM HYDRARGYRI COMPOSITUM, 12 per cent.

UNGUENTUM HYDRARGYRI DILUTUM, dilute ointment of mercury, 10 per cent of mercury in simple ointment.

UNGUENTUM HYDRARGYRI NITRATIS FORTE, citrine ointment is used, diluted with oil or lard, in conjunctivitis, and also as an application to syphilitic sores and gangrenous ulcers; it is acid and strongly irritant. 6.7 per cent.

UNGUENTUM HYDRARGYRI NITRATIS DILUTUM, citrine ointment diluted to one part in five.

UNGUENTUM HYDRARGYRI OLEATI, 25 per cent in simple ointment.

UNGUENTUM HYDRARGYRI SUBCHLORIDI, 20 per cent in simple ointment.

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VIII. MINOR METALS

Gold

Gold has been used at various times as a therapeutic agent generally for fantastic reasons. In recent years, however, it has been subjected to more scientific scrutiny, especially as a possible remedy for tuberculosis, lupus erythematosus, and arthritis. Its use in tuberculosis has been abandoned and its value in rheumatoid arthritis is still in the experimental stage. On the other hand, the administration of gold salts has found a place in the treatment of certain cases of lupus erythematosis. In this disorder a gold salt is injected intravenously at weekly intervals beginning with 10 mg. and gradually increasing the dose to 50 mg. at which level therapy is continued with occasional rest periods. Gold is of value only in the fixed and afebrile types of the disease and is contraindicated when the disorder becomes disseminated. Recurrences are not uncommon.

Gold is most frequently used in the form of gold sodium thiosulfate. Other preparations which have been used are sodium aurothiosulfate **(Sanocrysin)**, 4-amino-2-aurothiophenol carbonic acid **(Krysolgan)**, sodium aurothiobenzimidazole carboxylate **(Triphal)** and gold sodium thiomalate **(Myochrysine)**.

Preparations containing gold are very toxic and their use is attended frequently with severe reactions which may terminate in death.

Of the disagreeable effects observed in human beings, the more common are rise of temperature, nausea, and vomiting, rashes, diarrhea, ulceration of the mouth, rectal spasm, and albuminuria. The dermatitis may be severe. Toxic hepatitis, purpura, aplastic anemia and agranulocytosis also occur.

When given by mouth, soluble gold salts acts as gastro-intestinal irritants and readily produce vomiting. Intravenously given they produce a fall in blood-pressure, due especially to dilatation of the mesenteric vessels. In chronic poisoning, loss of weight with ulceration of the stomach and intestine are the most conspicuous effects.

Platinum

Platinum resembles gold in its action, but is more poisonous. It is not used therapeutically.

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Chromium

Chromium is used in medicine in the form of chromic acid and the bichromate of potassium, which are both powerful oxidizing bodies in addition to their poisonous action as metallic oxides. The former property renders them more irritant and corrosive than most of the salts of the heavy metals. Chromic acid in particular is a powerful caustic, combining the action of a metallic oxide, an acid and a strongly oxidizing agent. Applied to the skin in substance it corrodes it, but is said to cause less pain than the more penetrating caustic potash. Even in dilute solution, the chromic salts and the acid act as skin irritants. In industrial poisoning by chromium, the chief symptoms are diffuse dermatitis, usually on the hands or forearms, frequently with deep perforating ulcers. These ulcers arise from any abrasion of the skin, and the cartilaginous septum of the nose is also a common seat of ulceration which eventually leads to perforation. They are due to the local action of the poison and not to its absorption; they are said to be almost painless. The inhalation of the dust leads to chronic bronchitis, while that swallowed and absorbed may give rise to nephritis.

Symptoms.—In acute poisoning, when a large quantity of the acid or of a salt is swallowed, the symptoms are those of gastro-intestinal corrosion, intense pain in the throat and stomach, vomiting and purging, with blood in the vomited matter and the stools, collapse, and frequently death. The mouth and throat are stained yellow, and the stomach and intestine exhibit the usual appearance of violent corrosive poisoning.

The general action of chromic preparations may be elicited in animals by subcutaneous or intravenous injection, or by the administration of smaller quantities by the mouth. The symptoms resemble those caused by the general action of other metals. In the mammal, weakness and slowness in the movements is followed by albuminuria, glycosuria, diarrhea, and vomiting. Sometimes twitching of the muscles or even convulsions are seen, and then the weakness passes into general paralysis. The heart seems little affected by chromium, but the blood-pressure falls. After death, the stomach and bowel are found congested, and the mucous membrane is necrosed and ulcerated in some parts, covered with ecchymoses in others. Hemorrhages are also found in other organs of the body, notably in the heart wall. The kidney is in a state of acute parenchymatous nephritis and may contain deposits of uric acid; albumin, casts, and often blood cells appear in the urine. In chronic poisoning interstitial nephritis is said to occur.

Chromii Trioxidum (U. S. P., B. P.), chromic acid or anhydride (CrO_3), forms crystals of dark purplish-red color and metallic luster, odorless, very soluble in water. When brought in contact with organic substances, such as alcohol, glycerin or sugar, it oxidizes them rapidly and often violently with explosion.

Chromic acid is used as a caustic application to malignant growths, condylomata, lupus and diphtheritic membranes, to a less extent as an irritant disinfectant. It has generally been applied by dipping a glass rod into a solution formed by allowing the crystals to deliquesce, or it may be fused on the end of a wire. It has also been advised in 5 per cent solution as an application to prevent perspiration of the feet and to harden the skin. Weaker solutions (0.1 to 1 per cent) may be used in ozena, leucorrhea, etc.

Manganese

Traces of manganese are found in the blood and tissues of man and animals as well as in plants. It is one of the trace elements essential for life, although its rôle in this process is unknown. In fowls a deficiency of manganese gives rise to perosis.

The salts of manganese in large quantities cause acute irritation of the stomach and intestine, like those of the other heavy metals, and a form of chronic poisoning has been described in workmen exposed to manganese dust; the symptoms

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are chiefly stolid mask-like features, hysterical laughter or grief, languor and sleepiness and similar psychical manifestations, and later motor disturbances which are exhibited in a spastic gait, tremor and twitching of muscles, or cramps and stiffness and increased tendon reflexes. These symptoms are ascribed to lesions of the basal ganglia of the brain and when they are developed, no recovery occurs, although the patient may live many years. Manganese is absorbed from the alimentary tract only in very small quantity, and it appears to resemble iron closely in its course through the tissues. Its general action has been elicited by the hypodermic or intravenous injection of double salts. In mammals large injections induce epileptiform convulsions, particularly in the rabbit and guinea-pig. Smaller quantities, which cause a less acute intoxication, induce in the dog nausea and vomiting, diarrhea, weakness, somnolence, stupor, and death from arrest of the respiration. The urine is often increased, and contains bile pigment, and, toward death, albumin and casts. The stomach and bowel present no congestion or ulceration in these cases. Manganese is found in the vomited matter and the stools, in the liver, kidney, and intestinal wall, to a less extent in the other organs. In acute poisoning in mammals the blood-pressure falls, from depression and paralysis of the vasomotor center, while the heart is affected only much later. In subacute poisoning the darker color of the urine indicates icterus, but this is much more marked when small quantities are repeatedly injected into the subcutaneous tissues, and chronic poisoning induced. In chronic cases the nephritis, which is shown in the acute poisoning by albuminuria, is also more developed, the inflammation commencing in the cells of the tubules but later involving the interstitial tissue, if the animal lives long enough. Manganese injected hypodermically is excreted chiefly by the intestinal epithelium, bile and to a less extent by the kidney. In small repeated doses it causes liver cirrhosis.

The only preparation of manganese used in medicine is potassium permanganate which is referred to later (p. 791).

Cadmium resembles zinc very closely in its effects, but is more toxic. In some ways it behaves like mercury in the system. It has been suggested that the illness which may occur in smelter workers is due to cadmium, which is always present as an impurity in zinc, and which is found in the liver in these cases. Poisoning characterized by acute gastro-enteritis has resulted from the ingestion of small quantities of cadmium dissolved by acid foods or drinks placed in containers made of this metal.

Nickel is of interest only from a toxicological point of view. Following the injection of nickel salts in mammals, the usual symptoms arising from the action on the intestine and kidney are accompanied by tremors and chorea-like movements, later by tetanus, and finally by paralysis. Nickel also causes a profound fall in blood-pressure resembling that from arsenic and apparently arising from direct action on the walls of the arterioles and capillaries. Strongly acid food may form nickel salts when it is cooked in vessels made of this metal, but no poisoning results, either because the quantity ingested is too small or because it is too slowly absorbed from the stomach and intestine. Nickel often causes a dermatitis in workers engaged in nickel plating (nickel eczema). This condition may also result from contact of the skin with objects made of nickel. The condition is characterized by an edematous exanthem with miliary vesicles.

The gas, nickel carbonyl, $Ni(CO)_4$, formed when CO is passed over finely divided nickel, has produced poisonous effects when inhaled, the chief symptoms in man being cyanosis, dyspnea with bloody sputum, edema of the lungs and later involvement of the nervous system.

Cobalt resembles nickel in its general effects and toxicity. It has the remarkable property of stimulating the bone marrow and inducing polycythemia when fed to rats. In certain areas of the world, sheep suffer from an anemia similar to that of chlorosis. The addition of small amounts of cobalt to the diet is curative of this condition. Cobalt is not one of the trace elements essential for the treatment of the milk anemia of rats nor has it been shown to be essential for hemoglobin formation in any condition except the one noted above in sheep.

Tin salts paralyze the central nervous system in the frog, and later the heart.

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In mammals diarrhea, colic, vomiting and general weakness are observed, along with paralysis of some parts of the central nervous system and stimulation of others, leading to ataxia, stiffness and irregularity of the movements and occasionally convulsions. The sulfide is said to be deposited in the lymph spaces of the intestines in the same way as in bismuth poisoning. General poisoning may be induced by the administration of the salts by the mouth, even when there is no corrosion of the mucous membrane. Tin is often present in preserved foods containing acids, from being dissolved off the vessels, and is certainly absorbed, for it has been detected in the urine after the use of such articles. Apparently it is not often present in sufficient quantities to induce poisoning, for although some cases of "tin poisoning" are met with in medical literature, in none of them has it been satisfactorily established that tin was the cause. Chronic poisoning from this cause is unknown, and animals present no symptoms from prolonged treatment with larger quantities of tin than are contained in any preserved foods.

Thallium is a highly toxic metal and many cases of poisoning have resulted from its use as a depilatory, exposure to the metal in industry and the accidental ingestion of thallium-containing rat poisons. Thallium salts produce no immediate effects beyond a relaxation of plain muscle, *e. g.*, of the bronchi and uterus, but have remote and delayed effects that are unique, as when injected or ingested they cause shedding of the hair in all animals. This action, discovered by Richet, was the basis for its use in the treatment of ringworm but its use as a depilatory in this condition has been abandoned in favor of the roentgen-ray. When 8 to 9 mg. of thallium per kilo is given as a single dose by mouth, the hair of the scalp begins to loosen about the seventh day, and to fall out dramatically on the fourteenth. It is complete by the nineteenth, and soon begins to grow again. Hair on regions other than the scalp is more resistant and does not fall out with this dosage. The depilatory dose is dangerously near the toxic dose.

The toxic symptoms which may occur in chronic thallium poisoning are joint pains, especially in the lower limbs, peripheral neuritis, albuminuria, mental symptoms, hypochlorhydria, retrobulbar neuritis and stomatitis. The symptoms following acute poisoning occur within twelve to twenty-four hours after the ingestion of thallium salts and are referable mainly to the gastro-intestinal and nervous systems.

Thallium stimulates the autonomic reflexes, especially of the sympathetic, much in the same way as strychnine facilitates spinal reflexes (Dixon).

Vanadium has given rise to poisoning in workmen in various industries in which it is used. These consist of diarrhea followed by severe constipation, anemia, emaciation and some indefinite nervous disturbances; albumin, casts, and blood often appear in the urine. Cough is a prominent and characteristic symptom which may terminate in hemorrhage from the lungs. Lesions are found in the lungs, kidneys, liver, and intestinal tract. The symptoms observed in acute poisoning in animals resemble those induced by the other irritant metallic poisons. Jackson states that the intravenous injection of the vanadates in animals causes a sharp rise in the arterial pressure from constriction of the peripheral vessels; this arises from an action on the muscle wall of the arterioles for the most part, though the myoneural junctions may also be involved. The intestinal walls and the bronchioles are similarly aroused to contraction by vanadates.

Molybdenum and **Tungsten** resemble each other closely and induce typical metallic poisoning.

Uranium, in addition to the ordinary features of metallic intoxication, causes nephritis, edema and some glycosuria, the sugar often amounting to 1 per cent in the urine. In addition, dropsy occurs in animals poisoned with this metal, from the changes in the renal tubules, as well as from a destructive effect on the smaller vessels. Uranium also exerts a toxic action on the liver (MacNider).

Selenium and **Tellurium** are classed along with sulfur in chemical systems, but the salts of telluric, selenious, and selenic acid induce symptoms resembling those of the heavy metals and arsenic in many points, and may be inserted in

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this series. In mammals vomiting, purging, somnolence, dyspnea, tonic and clonic convulsions have been noted, and the stomach is found somewhat reddened, the mucous membrane of the intestine swollen and dysenteric, while the kidneys seem less affected. The perspiration is prevented by tellurates, apparently from paralysis of the terminations of the secretory nerves similar to that induced by atropine. Loss of hair occurs in rats receiving tellurium in their diet. An early symptom of poisoning with these bodies is a garlic odor in the breath, and many of the organs are found of a grayish color after death, and possess this odor. Hofmeister has shown that these salts are reduced to metallic selenium and tellurium in the body, and that afterward methyl compounds ($Te(CH_3)_2$, $Se(CH_3)_2$) are formed. These are volatile, and, excreted by the lungs, urine and feces, give the disagreeable odor. The synthesis of methyltellurium is one of the few known cases in which a compound with methyl is formed in the animal body, and is of some biological importance. All the selenium and tellurium is not excreted in this form, for some of it appears in the urine, and probably in the feces, in other combinations.

Selenium causes a disease in livestock, "alkali disease" or "blind staggers" in the Dakotas, Kansas, Montana, Wyoming, and other Western States where the soil and vegetation are high in selenium content. Appreciable amounts of selenium accumulate and deform the hooves of affected animals. This has been attributed to the replacement of sulfur which is present in high concentration in the hooves by the closely related element selenium. Acute selenium poisoning in cattle is also characterized by loss of vision, edema of the eyelids, lacrimation, and erosion of the bones. In chronic poisoning, growth is stunted, the body hair is lost and the animals become sterile. The human population in highly seleniferous areas also show a high incidence of gastro-intestinal symptoms and liver disease which has been attributed to the large amount of selenium ingested in the meat, eggs, milk and vegetables consumed (Smith and Westfall).

Selenium oxychloride is a highly toxic and powerful vesicant which induces painful ulceration when brought in contact with the skin.

Tellurates have been advised in therapeutics to prevent excessive sweating, and certainly have this effect, but are not to be recommended, as they are toxic and the strong garlic odor of the breath persists for days or even weeks after one dose.

It is estimated that the intake of selenium in the human in endemic areas is about 0.2 mg. per kilogram of body weight per day (Smith). This is deposited in all the organs but particularly in the liver. There is no evidence of poisoning in man under these conditions.

In animals toxicity varies and is dependent on other dietary factors. On a low protein, high carbohydrate diet poisoning is most apt to occur with resulting liver damage and serous effusions.

Osmic Acid has been recommended as an injection into the nerves in neuralgia. It is an intensely irritant substance, and seems to induce nephritis and diarrhea when absorbed. The greater part of the poison is, however, deposited as a black powder at the point of injection, owing to its being reduced by the tissues.

Germanium, on account of its close chemical relationship with arsenic, has been tried in experimental and human anemias but has been discarded as of no value.

Beryllium resembles aluminium in its effects but is more poisonous. It is absorbed from the alimentary canal and excreted by the kidneys and intestine. A type of poisoning with fever and rigors has been described in workers who inhale the vapor of beryllium fluoride.

The use of beryllium in the manufacture of copper alloys has made this metal of toxicological interest. A disease entity manifesting itself in dermatologic and respiratory tract manifestations occurs in workers in the beryllium industry. The skin disorders include dermatitis and chronic ulceration. When the respiratory tract is involved, the disease may progress to a diffuse chemical pneumonitis which may prove fatal. Preventive measures to eliminate fumes and dust are necessary to control the disease. (Van Ordstrand, *et al.*)

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Cerium was formerly used in therapeutics in the sickness of pregnancy and similar conditions, but is valueless for this purpose.

Radium is important in medicine because of its emanations which are destructive to tissue and are used in the treatment of cancer. The gamma radiations from the metal induce the same changes in the body as does irradiation with the *x*-ray. When radium is ingested it is stored in the bones similarly to lead and its toxic effects are due to the destructive effects of the alpha as well as the gamma rays. Megaloblastic erythropoiesis and leukopenia are followed by the development of osteogenic sarcoma of the bone. The toxic symptoms may not occur until several years after exposure to the metal.

Radioactive isotopes of various elements have been prepared in recent years and used in physiological experiments ("tagged" elements) as well as in experimental therapeutics. Radioactive phosphorus has been tried in the treatment of polycythemia and leukemia; radioactive iodine, in carcinoma of the thyroid. The value of such therapy is still undetermined.

Thorium.—The soluble thorium salts resemble those of aluminum in their local and irritant properties. Salts like the nitrate coagulate proteins, cause local sloughing when injected hypodermically, and intravascular clotting intravenously. The addition of sodium citrate prevents clotting. Hepatitis and cirrhosis of the liver have been described in rabbits after intravenous injection of thorium oxide. Late deposition of thorium may occur in the bones.

Thorium salts are radioactive and have been tried therapeutically for a variety of purposes. Thorium oxide (thorotrast) is used to cast an opaque shadow to roentgen-rays, especially in radiography of the liver and arteries.

Zirconium and **Haffnium** resemble one another in action and produce a fall of blood-pressure, stimulation, followed by paralysis of respiration and relaxation of the isolated rabbit's intestine (Neekirk).

Yttrium resembles aluminium in action. The chloride precipitates proteins. It produces paralysis in frogs, and excitement, dyspnea and later paralysis in mice.

Vincke and Oelkers have found that salts of the rare earths, *e. g.*, neodymium, lanthanum, praseodymium, yttrium and cerium, when injected into the blood stream, cause an incoagulability of the blood that may last several hours. Large doses of these metals cause necrosis of the liver and hypoglycemia (Fischler and Roecke).

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B. THE METALLOIDS

I. BISMUTH

THE insoluble salts of bismuth have long enjoyed a reputation in the treatment of gastric and intestinal irritation, and have been advised in surgery as applications to granulating wounds. Intramuscular injections of bismuth have been widely used in the treatment of syphilis, where they have replaced the more toxic mercury.

Symptoms.—The official bismuth salts are almost completely insoluble in water and consequently do not immediately precipitate proteins as

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do the soluble salts of the heavy metals. Indeed what local action they exert seems to be due almost entirely to the mechanical effect of a fine insoluble powder. They are used externally as dusting powders, when they absorb moisture and possibly toxins and have a sedative and protective action. Applied to ulcers or wounds, they have a slight antiseptic action, again largely mechanical, though possibly, under certain circumstances, small amounts of insoluble bismuth salts may go into solution when allowed prolonged contact with the body tissues, and they may thus have an antiseptic action similar to that produced by the insoluble salts of the heavy metals. When ingested in therapeutic doses, they induce no marked symptoms, even after prolonged use. They have little or no taste, and pass through the stomach and intestine for the most part unabsorbed, as both the oxychloride which is formed in the stomach and the sulfide formed in the intestine are likewise insoluble. So given, they coat the internal surface of the stomach and intestine and act as sedatives and allay gastric and intestinal irritation. They do not seem to affect the passage of food through the stomach in most cases. In the intestine they often cause some constipation. They give the stools a black color, due to the formation of sulfide of bismuth, which, by the removal of soluble sulfides, also tends to check diarrhea.

Toxicity.—Very little of the bismuth swallowed is absorbed, but traces appear in the urine of patients treated with it internally, so that some evidently passes into the blood. Enormous quantities of the insoluble bismuth compounds have been administered internally, especially in roentgen-ray examination of the stomach and intestine, without any symptoms of poisoning being elicited, but in one or two cases some stomatitis has occurred, while in other instances large concretions of bismuth have been found in the stomach and bowel. In a few cases fatal poisoning has occurred from nitrites being formed from the nitrate and leading to the formation of methemoglobin in the blood cells. This danger may be avoided by using the carbonate instead of the subnitrate. Some of the older writers describe serious poisoning from bismuth, but this was not due to the drug itself, but to the lead, arsenic, or antimony with which it was contaminated. A symptom formerly noted in cases treated with bismuth was an extremely disagreeable odor in the breath, but this has been shown to be due to the presence of tellurium in the preparation. Since its use was extended to wounded surfaces, and in the treatment of syphilis several cases of serious intoxication have occurred. The symptoms are salivation, stomatitis, swelling of the gums, tongue, and throat, pain and difficulty in swallowing, a black line along the gums or black patches in the mouth and throat, and gangrene of the soft palate and other parts of the mucous membrane of the mouth. Vomiting, diarrhea and albuminuria follow, but the patients generally recover when the dressing is removed from the wound or injections discontinued. Skin lesions with pruritus, erythema, urticaria, dermatitis and rarely hemorrhagic lesions may follow bismuth therapy. Systemic symptoms with malaise, nausea, headache, and vague bone and muscle pain and occasionally agranulocytosis with angina are observed. Jaun-

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dice, stomatitis, nephritis, and dermatitis are other complications encountered following therapy with bismuth.

Action.—The general action of bismuth has been studied in animals by the subcutaneous or intravenous injection of the double salts, such as the tartrate of bismuth and sodium. In frogs the symptoms are those of stimulation of the spinal cord and medulla oblongata, followed by depression and paralysis.

In mammals also large doses act chiefly on the central nervous system. The respiration is accelerated, the heart slowed, and violent clonic and tonic convulsions follow at short intervals, during which the movements are weak and incoördinated. Towards the fatal issue of the injection the heart often ceases entirely for some time and then regains its former rhythm quite suddenly. The blood-pressure falls, partly owing to the weakness of the heart, partly from depression of the vasomotor center. The cardiac effects—mainly a direct depressant action on the heart, with irregularities of which heart block is the commonest—have been described by Masson.

Smaller quantities injected intravenously or subcutaneously into mammals induce a more chronic form of intoxication, which resembles that seen in man. The earliest symptoms are loss of appetite, vomiting and diarrhea, salivation and stomatitis with ulceration of the gums, tongue, and buccal mucous membrane. Weakness, slowness and incoördination of the movements follow, and except in very few chronic cases, tetanic convulsions occur at intervals. The urine contains albumin and casts. The weakness gradually deepens into complete paralysis and the animal dies, generally without convulsions. The heart seems little affected in the chronic intoxication, but the blood-pressure is low from the intestinal irritation and general collapse.

Besides the stomatitis and ulceration of the mouth, the post mortem appearances of chronic bismuth poisoning in animals consist of some congestion, inflammation and necrosis in the kidney, and an intense black coloration of the cecum and the upper part of the large intestine. This pigmentation is limited very exactly by the ileocecal valve, and extends throughout the thickness of the bowel wall. The mucous membrane may also be necrosed in places and ulcers and hemorrhages are met within it. The black coloration is due to a deposit of bismuth sulfide on the mucous membrane and in the capillary vessels and lymph spaces. Meyer and Steinfeld found that bismuth is excreted all along the alimentary canal, but in larger quantities in the cecum and large intestine than elsewhere, and they ascribe the ulceration to the precipitation of the sulfide in the vessels and the consequent arrest of the blood current.

Bismuth is stored in the liver, kidneys, spleen, intestine and other organs, and is excreted by the urine, stomach, and intestine, but especially by the cecum and large bowel. It has been found in the saliva, sweat, milk and other secretions. It may pass through the placental circulation.

The action of bismuth in acute poisoning in animal experiments seems therefore to be exerted on the medulla and spinal cord, to a less extent on the heart, while in chronic intoxication the organs affected are those by which it is excreted —the mouth, kidney, and large intestine, especially the cecum.

Therapeutic Uses.—Bismuth salts are employed as dusting powders or ointments in the treatment of ulcers and skin diseases, when they act as protectives and mild astringents and antiseptics. The use of bismuth compounds as antiseptics is discussed under this heading (page 789).

Bismuth has been used in *gastric catarrh and ulcer*, where it acts simply as a protective powder with perhaps some astringent properties. It has been found that when swallowed it is at first deposited in the most dependent part of the stomach, but is later distributed evenly over the surface and forms a continuous sheet over any ulceration, which it thus protects from mechanical injury from the food, and also from the chemi-

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cal action of the gastric juice. The subnitrate has been largely used for this purpose, but the carbonate is to be preferred if an antacid action is desired. Bismuth has also been used in *diarrhea* for its astringent and protective action on the intestine, which is again due to its being deposited on the mucous membrane and acting as a mechanical coating over irritated surfaces. If bismuth is prescribed with alkalies, the carbonate should be used, as the subnitrate is slightly acid in reaction.

In 1916, Robert and Sauton used bismuth compounds in the treatment of rat trypanosomiasis and fowl spirillosis. Two years later, Kolle and Ritz demonstrated its effectiveness in experimental syphilis of rabbits and in 1921 Sazerac and Levaditi introduced the use of bismuth in human syphilotherapy. It has since then been extensively used and has largely replaced mercury as an adjunct to the arsenicals. Most bismuth compounds have little or no effect in syphilis when given by mouth; subcutaneous injections produce local irritation and are inadequately absorbed; intravenous injections are too toxic and too rapidly excreted; so that intramuscular injection deep in the gluteal region is at present considered to be the most generally dependable method of giving bismuth in syphilis. When so given, small amounts pass into the circulation and tissues, and destroy the spirochetes or inhibit their multiplication. It is not possible to get into the blood a concentration of bismuth sufficient to produce immediate and complete destruction of the organisms; and treatment aims rather at the prolonged maintenance of a maximum tolerated concentration. With a view to attaining this, a variety of compounds and preparations have been tried, including aqueous solutions of water-soluble compounds, aqueous suspensions, and solutions or suspensions in oils. As a rule soluble preparations are more rapidly absorbed, but are more liable to produce severe local reactions and toxic effects. The various preparations and their dosages are given in the accompanying table.

A good deal of agreement has been reached as to the relative values of arsenic, mercury and bismuth in syphilis. The organic arsenicals are most rapid in action and until the introduction of penicillin were considered preferable in the primary stages of the disease. Bismuth seems to be more rapid in action than mercury and less liable to produce toxic effects, so that it has displaced mercury in routine treatment. It is superior to mercury in tertiary and congenital syphilis. Like mercury it is of less value in neurosyphilis, though in locomotor ataxia it may produce definite subjective improvement. Bismuth in the basic form does not readily penetrate the cerebrospinal fluid, but Hanzlik has shown that, in the form of an anion, *e. g.*, as sodium iodobismuthite, it penetrates more readily.

Bismuth appears to have a spirocheticidal as well as a spirochetostatic effect. The optimal effects are obtained by the use of compounds which maintain a constant therapeutic level of the metal in the blood as reflected by the excretion of 2 mg. or more of bismuth in the urine daily. The oil-soluble preparations are believed to be more exact in their dosage than the insoluble suspensions and are absorbed and excreted less rapidly than the soluble bismuth compounds. The aqueous solu-

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tions, if injected two or three times a week maintain an effective concentration in the blood stream. Oil suspensions require less frequent injections (one weekly). Sobisminol mass, a complex compound obtained by the interaction of sodium bismuthate, tri-isopropanolamine and propylene glycol is intended for oral administration. It is intended for use in patients who are unable to undergo intramuscular therapy.

SOME BISMUTH COMPOUNDS USED IN THE TREATMENT OF SYPHILIS AND INCLUDED IN NEW AND NON-OFFICIAL REMEDIES (1945)

Common designation	Chemical designation	Dosage and mode of administration
Bismo-cymol	Basic bismuth camphocarboxylate in oil solution	0.1 gram of bismuth weekly or 0.05 gram twice a week for eight to ten weeks intramuscularly
Bismuth ethylcamphorate	Bismuth salt of d-camphoric acid mono-ethyl ester in oil solution	2 cc. (containing 80 mg. of Bi) weekly for ten to fifteen weeks intramuscularly
Bismosol	Potassium sodium bismuthotartrate in aqueous glucose solution	1 cc. of a 10 per cent solution intramuscularly every two days for 20 doses
Bismuth sodium tartrate	Basic sodium bismuth tartrate in aqueous solution	0.015 gram intramuscularly initially and 0.03 gram thereafter 3 times weekly for six to ten weeks
Potassium bismuth tartrate (U. S. P.)	Potassium bismuthyl tartrate in oil suspension or aqueous solution	0.1 to 0.2 gram of the oily suspension intramuscularly at weekly intervals until 2.4 to 3 grams has been given or 50 mg. of the aqueous solution 3 times weekly for twelve to eighteen weeks
Bismuth subsalicylate (U. S. P.)	Basic bismuth subsalicylate	0.1 gram intramuscularly in oil
Iodobismitol	Sodium bismuth iodide and sodium iodide in propylene glycol	16 to 20 injections of 2 cc. (corresponding to 0.025 gram metallic bismuth) every three days intramuscularly
Sobisminol mass	A complex of sodium bismuthate, tri-isopropanolamine and propylene glycol	2 to 3 capsules (each of which contains 0.15 grams bismuth) orally 3 times a day with plenty of water at 10 A.M.; 3 P.M.; and 8 P.M. for ten to twelve weeks
Sobisminol solution	As in preceding, but dissolved in water	2 cc. containing 0.04 gram of bismuth intramuscularly twice a week for ten to twelve weeks
Thio-bismol	Sodium bismuth thioglycollate in aqueous solution	0.2 gram 3 times a week intramuscularly for three to five weeks

In using bismuth in the treatment of syphilis careful observation is required for the appearance of toxic manifestations in the skin, mouth (stomatitis) and kidneys.

Bismuth is now chiefly used in syphilis as an adjuvant to arsenicals and as a substitute for mercury. It may be used alone in cases where

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the latter are contraindicated, *e. g.*, when syphilis is complicated by cardiovascular disease, nephritis or jaundice and in arsenic-fast or arsenic-intolerant individuals. Bismuth compounds are also effective in yaws. The metal has also been combined with arsenic in the form of bismarsen described on page 183.

Preparations

U. S. P.

Bismuthi et Potassii Tartras, a granular white powder, which darkens on exposure to light. Soluble 1 in 2 of water. Dose, 0.15 gram intramuscularly.

Bismuthi Subcarbonas, bismuth oxycarbonate, a white or pale yellowish-white powder, varying in composition; odorless, tasteless, insoluble in water or alcohol. Dose, 1 gram.

Bismuthi Subnitras, white bismuth, Magisterium Bismuthi, bismuth oxynitrate, a heavy, white, insoluble powder, odorless and almost tasteless, with a slightly acid reaction. It consists of a mixture of the hydrate and subnitrate of bismuth in varying proportions. Dose, 1 gram in powder or suspended in water.

Bismuthi Subsalicylas, the salicylate or oxysalicylate of bismuth, is a white, amorphous powder, insoluble in water. Dose, 1 gram, by mouth; 0.1 gram intramuscularly.

Injectio Bismuthi et Potassii Tartratis, a sterile solution in water or a suspension in a suitable fixed oil. Dose, 0.1 gram intramuscularly.

Injectio Bismuthi Subsalicylatis, a sterile suspension in oil. Dose, 0.1 gram, intramuscularly.

B. P.

Bismuthi Carbonas, the oxycarbonate or subcarbonate, a white powder, odorless, tasteless, insoluble in water. Dose, 0.6 to 2 grams.

Bismuthi et Sodii Tartras, a white powder freely soluble in water. By intramuscular injection. Dose, 0.06 to 0.2 gram.

Bismuthi Oxychloridum, a white powder, insoluble in water. By mouth, 0.6 to 2 grams; by intramuscular injection, 0.1 to 0.2 gram.

Bismuthi Salicylas, the subsalicylate. Dose, 0.6 to 2 grams; by intramuscular injection, 0.06 to 0.12 gram.

Bismuthum Precipitatum, a dull gray powder, easily diffusible in water. Dose, 0.1 to 0.2 gram intramuscularly.

Bismuthi Subgallas, the subgallate. Dose, 0.6 to 2 grams.

Injectio Bismuthi, 20 per cent of precipitated bismuth, in very fine powder, in a solution of dextrose, with some cresol. By intramuscular injection, 0.5 to 1 mil.

Injectio Bismuthi Oxychloridi, 10 per cent suspension in water solution of dextrose. By intramuscular injection, 1 to 2 mil. (15 to 30 min.).

Injectio Bismuthi Salicylatis, a 10 per cent suspension in olive or arachis oil, with some camphor and phenol. Dose, 0.6 to 1.2 mil.

Trochiscus Bismuthi Compositus. Each contains about 2¼ gr. of bismuth carbonate, with carbonates of magnesium and calcium.

Several new compounds of bismuth have been introduced in therapeutics, chiefly with the intention of combining the astringent properties of bismuth with the antiseptic action of benzol preparations. These have been used chiefly as dusting powders in various forms of skin disease, in burns and ulcers, in some ophthalmic conditions and after operations.

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II. ANTIMONY

Preparations of antimony have been used in medicine since antiquity and had a great vogue in therapeutics in the seventeenth and eighteenth centuries, being used empirically in a great variety of diseases. Because of its doubtful utility and great toxicity, its popularity declined until it was found to possess powerful trypanocidal properties. It has recently been shown to be effective in several tropical and other diseases, and is now scientifically established as a valuable chemotherapeutic agent. The salt most commonly used formerly was *tartar emetic*, or the double tartrate of antimony and potassium. As a double salt it is not readily dissociated and is therefore not so corrosive as the chloride, which is a powerful caustic when applied to the skin or the mucous membranes. More recently less toxic and more effective organic derivatives of antimony have been introduced and these have largely displaced tartar emetic in therapeutics.

Toxicology.—Industrial poisoning from antimony is of rare occurrence, but in recent years there have been several outbreaks of poisoning from the use of enameled vessels of inferior quality as containers for acid drinks, such as lemonade. Antimony oxide is sometimes used in the enamelling of hardware and is dissolved out by the tartaric or citric acid. Enamelled hollow-ware vessels obviously intended for other purposes may be dangerous if used for the preparation or storage of food or drink.

Chronic antimonial poisoning is very rare and difficult to diagnose. The symptoms are depression, headache, giddiness, and confusion, drowsiness, and indistinct sight. The appetite is bad, and the patient complains of heaviness, discomfort or pain in the region of the stomach, general weakness and exhaustion. Profuse diarrhea may be present, rapid loss of flesh, albuminuria, and finally collapse. Pustular eruptions have been observed from the prolonged internal use of tartar emetic. There is some reason to suppose that printers occasionally suffer from antimony poisoning arising from the presence of antimony in the type. In rabbits poisoned with tartar emetic, Franz found degenerative changes in the liver and kidney which were independent of capillary injury.

Many of the symptoms of antimonial poisoning, the profuse perspiration, salivation and, to some extent at least, the collapse which follows the ingestion of antimony salts, are manifestly secondary to the **Emetic Action**, and the cause of the vomiting. The older writers regarded it as arising from some central action, but there can be no question that it is the result of local irritation of the stomach; small quantities cause

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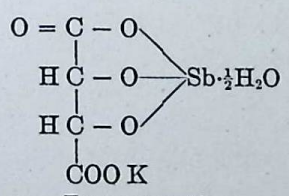
vomiting without any obvious lesion, but larger doses induce hyperemia and swelling of the gastric mucous membrane. Large quantities of antimony injected intravenously or subcutaneously also cause vomiting and purging, and this is apparently not due to its excretion into the stomach and bowel, for the movements occur in eviscerated animals; but much smaller quantities suffice to cause vomiting when given by the mouth.

In the stomach the antimony is slowly dissociated from the double salt and acts as an irritant; this liberation of the antimony ion may be aided by the acid reaction, but it also occurs when the reaction is rendered neutral, and in the intestine and skin, where the reaction is not acid. It is more irritant than arsenic and is absorbed more slowly, so that its action remains confined to the stomach, and as the vomiting removes much the greater part of the poison, the intestine remains unharmed except when large quantities have been swallowed and the emesis is insufficient from any cause. In chronic poisoning, ulceration of the small intestine is said to occur, especially around the solitary follicles and Peyer's patches.

TARTAR EMETIC

The double tartrate of potassium and antimony (tartar emetic) and its sodium analogue are the simplest and oldest salts of antimony used in medicine. When rubbed on the skin, tartar emetic causes redness and a papular eruption, which later passes into vesicles and pustules. If the application be further persisted in, these pustules may become confluent and form small abscesses, and later cause extensive necrosis and ulceration of the skin. The points of origin of the papules are the openings of the cutaneous glands and the hair follicles. When injected hypodermically, tartar emetic causes intense and lasting pain and very often suppuration and sloughing, which may involve the underlying muscles.



Tartar emetic

Symptoms.—Tartar emetic has a slight acid taste, and in very small quantities causes no symptoms, except some perspiration. In somewhat larger doses its ingestion is followed by nausea and vomiting, with very marked depression and the usual accompaniments of emesis, such as salivation, profuse perspiration and acceleration of the pulse (see Apomorphine, page 363). In antimonial poisoning the vomiting is violent and continuous, the ordinary contents of the stomach being first evacuated, and then a slimy mucous fluid, which may later contain blood. In some cases it is said that no gastric symptoms are observed, but these must be exceedingly rare. The vomiting is accompanied by profuse watery diarrhea, resembling that of arsenical poisoning,

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and by great muscular weakness and collapse. The pulse may be somewhat accelerated at first, but is weak, and later becomes slow and irregular. The skin is cold and covered with clammy perspiration, and cyanosis of the face and extremities is generally marked. The respiration is slow and may be irregular, the voice weak and husky, the temperature is depressed, and the patient falls into a comatose condition, which deepens, until after a few weak convulsive movements the respiration ceases. The urine is sometimes increased in the beginning of the poisoning, but later may become scanty or entirely suppressed. It often contains albumin.

The minimum fatal dose of tartar emetic is doubtful, as the greater part of the poison is generally removed by vomiting. Recovery has been observed after very large quantities, while in other cases 0.1 gram has proved fatal.

In the seventeenth century antimony in the form of tartar emetic was prescribed so widely and was believed to do so much harm, that the graduates in medicine of Heidelberg were required to take an oath never to use it. At present it is no longer used as an emetic since it is slow in action and induces greater depression and more prolonged nausea than the other drugs which are prescribed for this purpose, such as apomorphine or ipecacuanha. Tartar emetic alone is also rarely used now for its expectorant action in acute bronchitis in which the secretion of the bronchial mucous membrane is insufficient. It is included, however, in certain expectorant mixtures such as the **Compound Mixture of Opium and Glycyriza,** and the **Compound Syrup of Squill,** N. F. Although originally used in leishmaniasis, granuloma inguinale, biharziasis and other tropical diseases, it has been displaced to some extent in these disorders by the less toxic compounds now to be described.

OTHER ORGANIC ANTIMONY COMPOUNDS

The organic compounds of antimony used in medicine may be classified into two groups: (1) those in which antimony is trivalent and (2) those in which it is pentavalent. In addition to tartar emetic and its sodium analogue the trivalent antimony compounds include antimony thioglycollamide, antimony sodium thioglycollate and fuadin. The pentavalent compounds include stibosan, stibamine, urea stibamine and neostam. These derivatives have, to a great extent displaced tartar emetic in the chemotherapeutic treatment of the following group of diseases in which antimony is specific.

Granuloma Inguinale, a venereal disease (not to be confused with lymphogranuloma inguinale which is due to a virus infection), is caused by infection with a **Leishmania** organism. The so-called Leishman-Donovan bodies are found in the lesions which consist of reddish granulomatous patches which spread over the abdomen and thighs or may involve the cervix. The disease is not uncommon among the negroes of the Southern United States. **Kala Azar** (visceral leishmaniasis), **Oriental Sore** (cutaneous leishmaniasis), and **Espundia** (American leishmaniasis) are all diseases caused by protozoan parasites of the genus *Leishmania.* They are all effectively treated by antimony salts.

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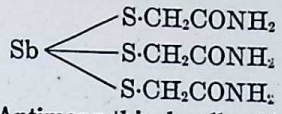
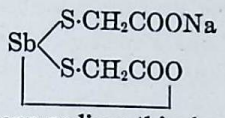
Another group of disorders against which antimony derivatives are specific is **Schistosomiasis** or **Bilharziasis**, which is caused by infection with flukes which invade the blood stream.

In the treatment of **Trypanosomiasis**, the pentavalent arsenic derivatives have replaced the antimony compounds.



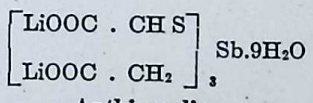
Antimony thioglycollamide



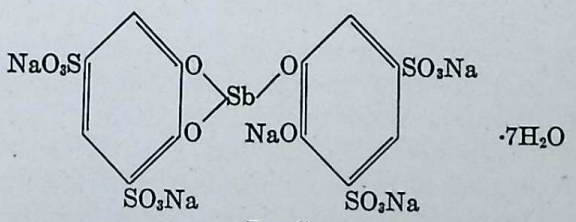
Antimony sodium thioglycollate

Antimony Thioglycollamide, the triamide of antimony thioglycollic acid and **Antimony Sodium Thioglycollate** are less toxic and less irritating than tartar emetic. Unlike the latter, which must be injected intravenously these compounds may be administered either intravenously or intramuscularly. The thioglycollamide is more toxic and less soluble than the thioglycollate but has the advantage of being more stable. Both compounds are used instead of tartar emetic in the treatment of **Lymphogranuloma Venereum** and **Kala Azar**. The thioglycollamide is given in doses of 0.08 gram dissolved in 20 cc. of sterile water every second day until 15 to 25 injections have been given. The thioglycollate is given the same number of times in doses of 0.5 to 0.1 gram every third or fourth day.

Another antimony compound closely related to the preceding drugs which has recently been introduced into therapeutics is **Anthiomaline, Lithium Stibiothiomalate,** which has been used in the treatment of **filariasis.**



Anthiomaline



Fuadin

Fuadin (stibophen), a derivative of catechol disulfonic acid is another of the trivalent antimony compounds introduced into medicine. It has largely replaced the previously mentioned compounds in the treatment of **Granuloma Venereum** and is also the drug of choice in the treatment of the intestinal stage of **Schistosomiasis.** Fuadin is injected intramuscularly in the form of a 6.3 per cent aqueous solution. One and five-tenths

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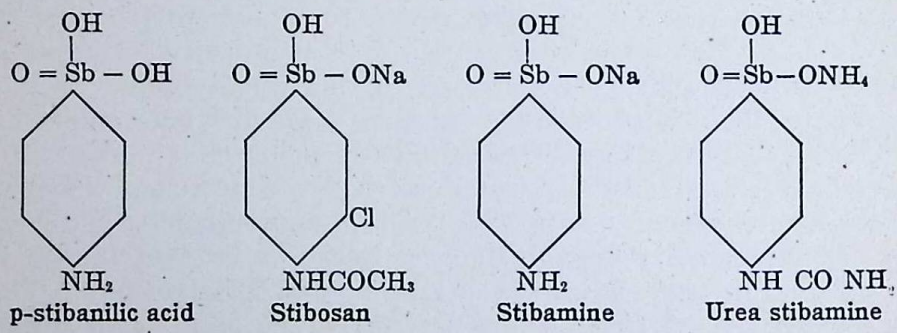
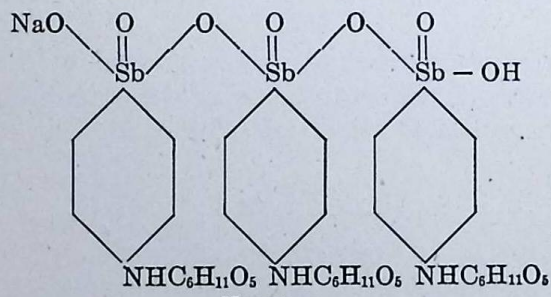
cc. are given on the first day; 3.5 cc. on the second, and 5 cc. every other day thereafter until a total of 40 cc. is given over a total period of fifteen days. In granuloma inguinale it is necessary to continue the treatment after all evidence of the disease has disappeared by repeating the course. Thereafter the drug is given once a week and then every two weeks to prevent relapse. In schistosomiasis, iron is indicated together with fuadin.

Pentavalent Compounds.—A number of pentavalent antimony derivatives have been used particularly in the treatment of leishmaniasis. These are derivatives of p-stibanilic acid. These compounds are less toxic and hence may be given in larger and less frequent doses. Fewer disagreeable reactions follow their use, but their cost compared to tartar emetic and the other trivalent compounds has militated against their more general use. A number of antimony compounds have also been prepared which are chemically related to arsphenamine but in which one of the arsenic atoms is replaced by antimony.





Neostam

The trivalent antimony compounds appear to be of possible value in the treatment of schistosomal infections, filariasis, onchocerciasis, Carrion's disease and other exotic tropical disorders. Neostibosan, the diethylamine salt of p-stibanilic acid has recently been found to be effective in the treatment of human filariasis (Culbertson *et al.*).

Following therapeutic intravenous injections of antimony salts, the following symptoms may occur: dry cough, frequently; more rarely, dryness of the mouth, a feeling of constriction of the throat or tightness of the chest, colicky pains in the abdomen and pains in the shoulder. The occurrence of giddiness, vomiting, or diarrhea calls for care with subsequent doses. Pneumonia, pains in the joints and bradycardia may follow a course of therapy.

In cases of **Antimonial Poisoning**, emetics are seldom required, but the

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stomach may be washed out by means of the stomach tube if vomiting is not present, and a purge may be given to remove the poison in the bowel. Tannic acid, lime or magnesia may be used to precipitate the antimony in the stomach, and potassium hexatantalate has also been advised for this purpose.

PREPARATIONS

ANTIMONII ET POTASSII TARTRAS (U. S. P., B. P.), tartar emetic, tartrated antimony ($KSbOC_4H_4O_6)_2.H_2O$), forms colorless, transparent crystals, or a white granulated powder, without odor, and having a sweet, afterward disagreeable, metallic taste, soluble in 17 parts of cold water, insoluble in alcohol. Dose, U. S. P., 3 mg.; B. P., as an expectorant, 0.002 to 0.008 gram; emetic, 0.03 to 0.06 gram; by intravenous injection, 0.03 to 0.12 gram.

ANTIMONII ET SODII TARTRAS (B. P.), whitish scales or powder, hygroscopic, soluble in 1.5 parts of water. Doses as of tartar emetic above.

STIBOPHENUM (B. P.), stibophen, sodium-antimony-bispyrocatechol-3:5-sodium disulphonate, $(NaO_3S)_2C_6H_2O_2{:}SbOC_6H_2(ONa)(SO_3Na)_2 7H_2O$. Dose, intravenously, 0.1 to 0.3 gram.

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III. ARSENIC AND ITS INORGANIC PREPARATIONS

Some of the less active preparations of arsenic, such as the sulfides, Realgar (As_2S_2) and Orpiment (As_2S_3), have been known in therapeutics since the beginning of the Christian era, but this metal was brought into especial prominence in later times through the frequent use of the more dangerous oxides in criminal poisoning. Thus the notorious Aqua Tofana of the sixteenth and seventeenth centuries owed its activity to the presence of arsenic, and various arsenical compounds were formerly used more largely than almost any other poison in suicide and homicide. This is to be explained by their having been widely employed in the arts and for such purposes as insecticides, and thus being readily accessible to all. There was, moreover, a general recognition of their poisonous nature and being tasteless they could be administered to the victim without arousing suspicion. Of late years intentional arsenic poisoning has become somewhat less common, though, on the other hand, accidental poisoning is still met with not infrequently, especially in the chronic form. Many of these chronic cases are extremely difficult to diagnose, and probably often pass unrecognized by the attending physician. In view of this fact, it seems desirable that more stringent measures should be taken to reduce the use of arsenic in

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the arts, and especially to prevent its being brought in contact with food. The danger of the use of the green arsenical dyes, such as Scheele's Green (arsenite of copper), and Schweinfurt's Green, or Paris Green (arsenite and acetate of copper), is now generally recognized, but arsenic is still used in the preparation of other colors, and these may give rise to poisoning. It is widely used as a spray upon grape vines, fruit trees and other plants to preserve them from the attacks of insects. Poisoning has occurred from these sources and is difficult to diagnose, as it is in some cases impossible to find the means by which the arsenic enters the system. A widespread epidemic of poisoning in England in 1900 drew attention to a source of arsenic which up to that time had not received the attention it merited. Several thousands of persons suffered from arsenic being contained in cheap beers made from glucose, in the manufacture of which sulfuric acid had been employed. The sulfuric acid was formed from iron pyrites containing arsenic, and the poison was carried from the sulfuric acid with the glucose into the beer. Sulfuric acid is used in the manufacture of so many drugs, foods and other substances in constant use, that this intimation that it may convey arsenic into articles where its existence has not hitherto been suspected, is of the gravest importance. Arsenic poisoning also occurs as a result of exposure to the metal in industry, particularly in the metallurgical trades.

Metallic arsenic is insoluble in water, and passes through the alimentary canal for the most part unchanged and without action, but it is possible that small quantities may be oxidized to arsenious acid in the stomach and intestine under some conditions. Some symptoms have been observed when it is rubbed on the skin in a state of fine division, and these are probably due to its absorption in the form of an oxide. The characteristic "arsenic" action is induced by the salts of trivalent arsenious acid (H_3AsO_3), and by its anhydride (As_2O_3), which is often known as arsenic, and which exists in the tissues as arsenites. Arsenic action is therefore due, not to the element, but to the ion of arsenious acid. The anhydride and salts of the pentavalent arsenic acid (H_3AsO_4) cause similar symptoms, but are less poisonous and act more slowly than those of arsenious acid, and probably owe their effects to their being changed to arsenites in the tissues. The action being due to the ion and not to the element, it necessarily follows that compounds from which the ion is not liberated do not induce the arsenic action, or do so only when they are changed to bodies which can dissociate the arsenious acid ion. Thus organic arsenic combinations in which the metallic atom is directly attached to carbon are only feebly poisonous, but in course of time seem to be changed to arsenious acid in the tissues, and then cause typical poisoning.

Arsenious acid, which in the following pages will be taken as the representative of "arsenic" action, has a faint sweetish taste, and is therefore not so likely to be detected by the victim as many of the other poisons.

Symptoms.—In large quantities arsenic very often causes no symptoms for one-half hour or more, but then the patient complains of a feeling of constriction in the throat, of difficulty in swallowing, and

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of discomfort in the stomach region. This soon increases to violent pain, and is accompanied by vomiting, and later by watery diarrhea. The stools are at first of ordinary diarrheic appearance, but later resemble the "rice-water" stools of cholera, in that they consist almost entirely of minute shreds of disintegrated mucous membrane suspended in a serous fluid; sometimes, however, they are clear and gelatinous in appearance. In some cases, blood appears in the vomited matter and also in the stools, but this is not by any means an invariable feature. The urine is diminished, or entirely suppressed, from the great amount of fluid eliminated by the stomach and bowel. These symptoms from the alimentary tract are accompanied by giddiness, cramps in the muscles, headache, and soon by collapse, with cold damp skin, pallor, feeble pulse and weak, sighing respiration; this later passes into coma, and death follows with or without convulsions. In cases in which the dose is smaller than the fatal one, or in which much of the poison is eliminated by vomiting, the patient may recover without further symptoms than those already described. Frequently, however, he recovers from the acute symptoms only to develop those of chronic arsenical poisoning. In some instances it is said that no symptoms are present except those of collapse and coma. In acute poisoning, death may occur within twenty-four hours, but more frequently the patient lives for two to four days or longer, and then succumbs to exhaustion. The fatal dose is uncertain, because arsenic is very insoluble, especially when in coarse particles, and thus large amounts (2 grams) have been swallowed in solid form with impunity and have been recovered from the stools unchanged; even when more soluble preparations are taken, much may be rejected by vomiting. Fatal poisoning has occurred from about 0.1 gram of arsenic in solution.

Chronic Arsenic Poisoning may arise from a single large dose, the effects persisting for weeks or months after the ingestion and new symptoms arising as the earlier ones disappear; more frequently, however, it is induced by the prolonged absorption of small quantities. The milder symptoms may arise from its therapeutic use, but typical cases are generally due to the presence of arsenic in the form of dyes in wall paper, carpets, or clothes, or in stuffed animals in the rooms inhabited by the victims, or to the constant handling of arsenical pigments and other compounds in mines and manufactories. Widespread poisoning has been observed from the use of wines containing arsenic at Hyeres in France, from milk diluted with arsenical water in London, and from beer in the Manchester district. In these last cases the arsenic was in solution, but it often seems to be inhaled in the form of fine dust, which falls from the walls or other objects.

The symptoms of chronic arsenic poisoning, which are often very obscure, may be divided into three phases. In the *first* of these, the patient complains of weakness and languor, loss of appetite, some nausea and occasionally vomiting, with a sense of heaviness and discomfort in the stomach. Diarrhea may be present, but is often absent, and in fact some constipation may occur.

In the *second* phase the conjunctiva is often red and inflamed, and symptoms of coryza appear, with sneezing, hoarseness and coughing, from a catarrhal condition of the mucous membranes of the nose and larynx. Some swelling of

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the liver and jaundice may occur, but these are not generally well marked. Skin eruptions of various forms—papular, vesicular, or erythematous—are generally noted; very often the epidermis falls off in fine brownish scales, or, in the hands and feet, in large flakes (keratosis); a curious pigmentation is very common, the skin assuming a dark metallic color resembling in extreme forms that produced by rubbing a lead pencil upon it (arsenic melanosis). This pigmentation is much more marked in persons of dark complexion than in fair people, in whom it may be indistinguishable from ordinary freckles; it generally disappears when the patient is removed from the poisonous atmosphere, but has been permanent in some cases. In prolonged poisoning the eruptions may simulate almost any form of skin disease, and the hair and nails fall off. Herpes is not infrequently observed and points to nervous disturbances such as are prominent features in the next phase.

These phases are not always distinct in cases of poisoning, and very often some of the symptoms of the second phase may appear before any marked disorder of the digestive tract. In the prolonged therapeutic use of arsenic, the first indications of commencing poisoning are redness, itching, suffusion and swelling of the conjunctiva and eyelids, and dryness of the nose and throat, as in coryza. On the other hand, in workmen exposed to arsenical dust, the first symptoms may arise from the skin or from bronchial irritation.

The *third* phase is marked by disturbance of sensation and motion in localized areas, generally in the hands and feet (peripheral neuritis). It is often ushered in by intense persistent headache or by acute pain located around the knee, ankle or foot, less frequently in the wrist and hand. The patient complains of formication in the extremities, and of the discomfort caused by the pressure of the bed-clothes on the feet and legs. The palms of the hands and the soles of the feet are often red, swollen and extremely sensitive to touch (erythromelalgia), and pressure on the muscles induces the most intense pain. Later, sensory paralysis may set in, especially in the extremities, and the less acute sense of touch in the feet and hands induces symptoms resembling those of locomotor ataxia. The sensitiveness to heat and cold may be exaggerated or dulled, or sometimes heat is not appreciated, while cold causes intense pain. The sense of pain varies in different cases, in some being abnormally acute, in others deadened. These sensory disturbances are followed in severe poisoning by motor paralysis, which generally appears in the extensor muscles of the toes, later in the peronei muscles. More rarely the flexor muscles of the leg and foot are involved, and in some cases the affection commences in the extensors of the hand and fingers. As a general rule the paralysis is confined to the extremities, but in some cases it has been found to invade the trunk. It is generally, but not invariably, symmetrical, and the muscles affected atrophy rapidly, and present the reaction of degeneration. There is sometimes some difficulty experienced in diagnosing arsenic from lead paralysis, but in the former there is often a history of acute poisoning, while the latter is almost invariably due to prolonged absorption. Disturbances of sensation are much more common in arsenic than in lead palsy, and in the latter the forearm muscles are generally affected first, in the former, those of the leg. In arsenic poisoning atrophy is said to occur more rapidly, and there is no line on the gums. Another condition which presents still greater difficulties in diagnosis is alcoholic neuritis. But in the latter, skin eruptions are rare, coryza is not present, and there are generally more marked brain symptoms than in arsenical cases. In doubtful cases the urine and the hair of the patient should be tested for arsenic. Arsenic paralysis may appear as early as three days after an acute intoxication, but is commonly observed later, and may occur only after three or four weeks.

In very prolonged arsenic poisoning the patient may sink into an apathetic, semi-idiotic condition, or may become epileptic. In most cases the symptoms slowly disappear when the poison is removed, but even slight paralysis may last for many years before it is entirely cured, and after complete degeneration of the muscles little improvement is to be expected. The contractures which follow are generally due to the unopposed action of the sound muscles, but sometimes arise from the shortening of the paralyzed ones.

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Arsenical poison occurs industrially from inhalation of, or contact with, the dust of compounds of arsenic, showing itself often in skin eruptions, or more rarely in cancer of the skin, especially where the dust alights on folds of skin or moist surfaces like the groin. Other symptoms of chronic arsenical poisoning may be present, due to absorption of arsenic, conjunctivitis and hoarseness being frequently early symptoms. Perforation of the septum of the nose is not uncommon. The frequency of poisoning from this source has been greatly diminished by measures taken to protect the workers, *e. g.*, by use of exhaust draughts.

Action.—Arsenites and arsenious acid do not coagulate proteins or change them in any way, except when applied in such enormous quantities as never reach the stomach, so that the action of arsenic on the **Alimentary Canal** cannot be explained as due to any ordinary form of corrosion, although the symptoms and the postmortem appearances resemble in many points those of the corrosive poisons. Thus the mucous membrane of the stomach is generally found red and swollen, and often contains hemorrhages. The epithelial coat can be rubbed off very easily, and is found to be in a state of fatty infiltration, and sometimes resembles a false membrane; or the only lesion may be cloudy swelling and fatty infiltration of the gland-cells.

The intestine presents very similar appearances, the mucous membrane being swollen and congested, more especially around Peyer's patches. It contains a quantity of thin fluid with flakes of membrane, resembling exactly the rice-water stools of cholera, from which it is difficult to distinguish it.

The same symptoms arise when arsenic is absorbed from the subcutaneous tissue, or from the broken skin, though only traces of arsenic are found in the contents of the stomach and intestine when it is ingested in this way.

The failure to explain the gastro-intestinal action of arsenic by ordinary corrosion has led to the suggestion that it is due to the extreme dilatation of the intestinal vessels, which gives rise to the congestion and swelling, and this in turn to the destruction of the lining membrane, perhaps by the exudation of fluid beneath the epithelium. This transudation of fluid is certainly in accord with the watery character of the stools in arsenic poisoning, but the explanation does not seem entirely satisfactory, for it fails to account for the fatty infiltration and the cloudy swelling of the epithelium, which are in some cases the only lesions found here. The fatty infiltration is not confined to the stomach and bowel, but involves a number of other organs, although it is not as a general rule so widely distributed as in phosphorus poisoning. Arsenic then must be considered to have a specific action in causing fatty infiltration of the epithelium of the stomach and intestine. This in itself is sufficient to explain many of the symptoms from these organs, although it may well be that the vascular action is the cause of the excess of fluid in the intestine, and in fact, the fatty infiltration alone is insufficient to explain this feature, which is absent in phosphorus poisoning.

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In therapeutic doses arsenic is said to increase the appetite and promote digestion, an effect which may perhaps be due to the specific action on the epithelium, this in its milder forms proving of advantage to the organ, though in excess it leads to its degeneration; it has been observed in dogs with gastric fistulæ that the gastric secretion is augmented by small quantities of arsenic.

Circulation.—In the frog the heart is slow, weak, and irregular, and ceases in diastole after comparatively small doses; the action seems to be a direct paralysis of the muscle. In the mammal the heart is little affected by arsenic, but a very marked fall of the blood-pressure follows the injection of large doses intravenously. This is due to dilation of the capillaries from a direct action on their walls; epinephrine and nicotine continue to raise the blood-pressure after arsenic, because the arterial wall can still respond to strong nervous impulses; the vessels of the splanchnic area seem more susceptible to this arsenic action than those of the rest of the body, and their dilation leads to very marked congestion of the stomach and bowel, and reduces the blood-pressure to zero. The dilated capillaries permit the passage of fluid into the tissues more readily than normally, and this explains the appearance of edema in cases of poisoning and also the large amount of fluid in the stools and vomited matter. Arsenic is therefore often termed a capillary poison.

Respiration.—In cases of poisoning in man the respiration does not seem to be much affected until late, but it ceases before the heart, probably from the exhaustion and low blood-pressure, and not from any specific action on the center.

The action of arsenic on the **Central Nervous System** has been repeatedly examined. A descending paralysis is elicited in the frog, the animal first losing its spontaneous movements, and then its reflexes, and the terminations of the motor nerves being involved only very late in the intoxication. In mammals there are generally no certain indications of direct action on the nervous system in acute poisoning, for the weakness and prostration, and the final loss of consciousness and coma may be attributed to the exhaustion from the gastro-intestinal effects rather than to the centers being immediately affected.

The pathology of the nervous disturbances observed in chronic poisoning, and often after a single large but not immediately fatal dose, bears no relation to the effects observed in animals in acute poisoning. The symptoms in chronic poisoning all point to peripheral neuritis as the cause, and the characteristic lesions in the nerve trunks have been shown to occur both in man and animals exposed to the prolonged action of arsenic. In severe cases the spinal cord may also be involved secondarily. The peripheral muscles and nerves are little affected in acute poisoning.

The unbroken **Skin** is not affected by arsenic, unless when it is applied repeatedly or allowed to remain in contact with it for some time, when it may give rise to redness, pustules or vesicles and later to violent erysipelatous inflammation. It has not, however, any such corrosive action on the skin as is possessed by strong acids, and the subcutaneous injection of arsenic is not painful at first. It is more active when applied

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to denuded surfaces and to the mucous membranes, destroying them to some depth and causing acute pain, but even here it acts more slowly than ordinary caustics. According to Ellinger, the local "corrosive"

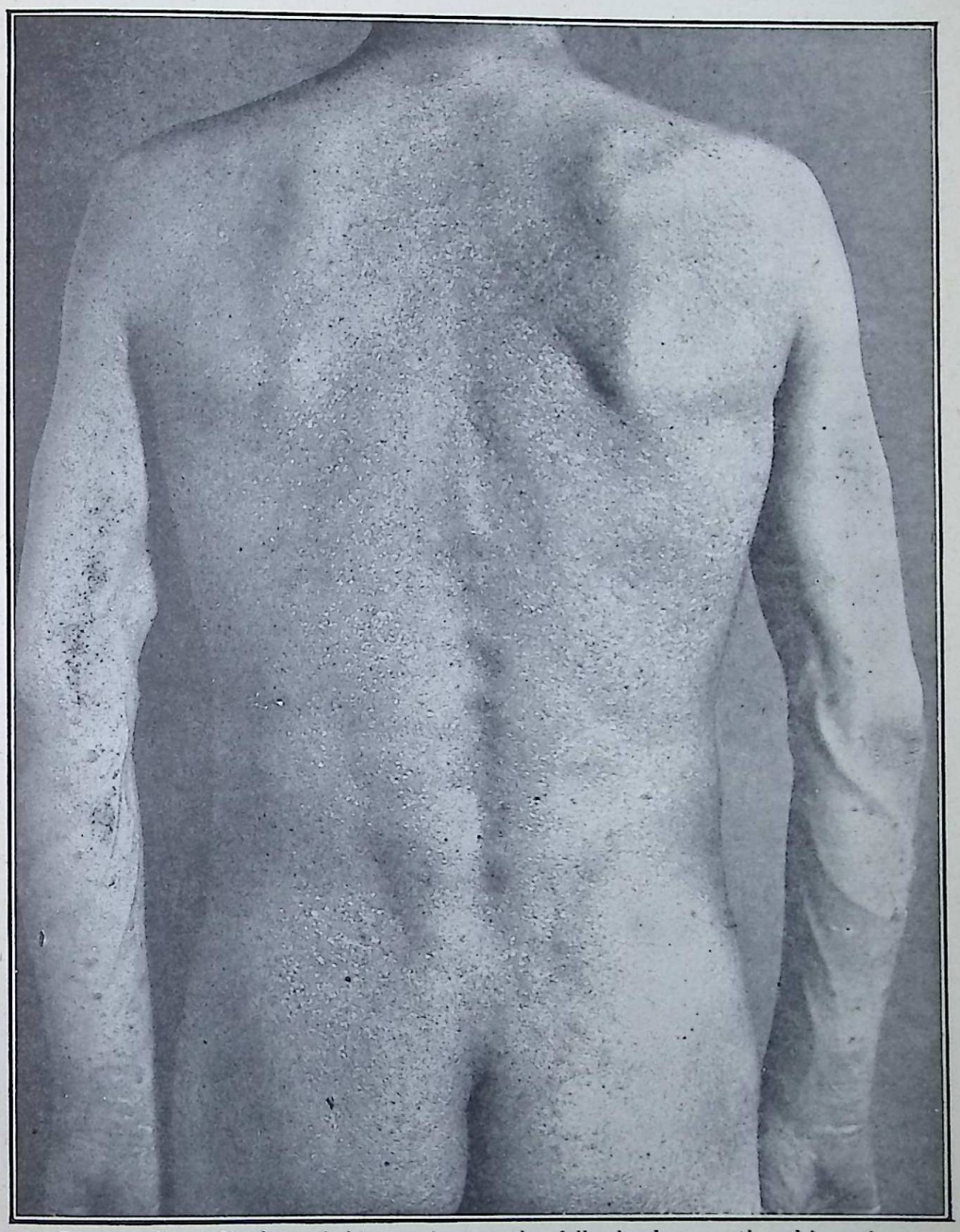

FIG. 6.—Generalized mottled hyperpigmentation following long-continued ingestion of arsenic. (Fordyce & MacKee.)

action of arsenious acid is due to a primary injury to the capillaries, which leads to cell death by loss of circulation. The local effects of arsenic on the skin are seen only in workmen handling arsenic, as in

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color factories, in which affections of the skin of the face, hands and scrotum are by no means rare.

In chronic arsenic poisoning skin eruptions are common, and are to be ascribed to the direct action of the drug on the skin. This appears to accelerate the growth and proliferation of the epithelium, which is found to be increased in thickness, but which in very severe cases shows signs of atrophy and degeneration. Arsenic has been found in appreciable amount in the hair and epidermal scales, and in the fluid of a blister in patients treated with it, and changes in the condition of the skin in animals have also been observed.

The melanosis of arsenic poisoning seems to be due to the deposition not of an arsenical compound, but of some organic product in the deeper layers of the corium. The symptoms of irritation of the mucous membranes of the eye, nose and larynx are analogous to the skin eruptions.

The action of arsenic on **The Blood** is still obscure. It was formerly frequently prescribed in the treatment of anemia but its value is questionable. In pernicious anemia the administration of arsenic may be followed by a definite reticulocyte response but an increase in the number of mature red cells is less often encountered. In chronic myelocytic leukemia arsenic decreases the white cell count and improves the anemia.

The **Metabolism** is affected by a poisonous dose of arsenic in the same way as by phosphorus, but the alteration is not generally so marked and is liable to be overlooked, owing to the more intense action on the alimentary canal. The nitrogen of the urine is considerably increased due to a break down of body tissues. The glycogen of the liver disappears entirely, and the liver seems incapable of forming it from the sugar of the food. Lesions of the medulla oblongata (puncture diabetes) do not cause glycosuria after arsenic, but curare and other drugs are still capable of eliciting this symptom. The fatty degeneration of the epithelium of the stomach and intestine has been mentioned already, but this alteration is not confined to these tissues, being found in the liver and kidney, in the muscle cells of the heart, blood-vessels and striated muscles, and in the lining epithelium of the alveoli of the lungs. Small necrotic foci have been observed in the liver, along with signs of active division of the parenchymatous cells, as in phosphorus poisoning. Szent-Györgi ascribes the changes in metabolism produced by both arsenic and antimony to interference with tissue respiration and Oelkers finds that arsenic inhibits the action of ferments on protein and fat metabolism.

The fatty infiltration may have the same results as in phosphorus poisoning. The liver is somewhat enlarged and the pressure on the bile ducts prevents the escape of bile into the intestine, and thus induces jaundice and appearance of bile pigments and bile acids in the urine. Jaundice is seldom, however, a very marked feature in arsenic poisoning, and is often entirely absent. The bile is said to contain albumin, red blood cells, and casts, as in phosphorus poisoning, but does not present other changes except immediately before death.

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The prolonged administration of arsenic in quantities insufficient to produce chronic poisoning is reputed to have some effect on the **Growth and Nutrition**, but while improved nutrition is attested by a number of the older observers, other equally careful investigators have not been able to confirm their results. Thus Stockman and Greig observed no change in the growth of animals under prolonged treatment with arsenic, and found that the only tissues affected were the growing bones, which appeared denser than usual. Sollmann, feeding rats with very small quantities, far below the corresponding therapeutic dose in man, found that these tended to lessen appetite and retard the growth of the animals. The results of these careful researches are thus opposed to the popular view that arsenic is a "tonic" and exercises an invigorating action on the nutrition in man.

Another widely held view is that the habitual use of small quantities of arsenic leads to **Tolerance**, and that the dose may be gradually increased until it far exceeds that which would be poisonous in ordinary persons. This is given as the explanation of arsenic-eating, a practice which has existed in different parts of the world, but which was most widespread and best known in Styria and the Tyrol. The peasants there believe that it enables them to work better, and particularly to climb the mountains with less effort and less respiratory distress. Knapp administered 0.4 gram of arsenious acid to one of the peasants at Graz without inducing any effects whatsoever. Arsenic-eating is said to be indulged in to a considerable extent in young women in some countries with the object of improving the complexion and figure, and cases of arsenic habit have been described in different parts of America and elsewhere. As far as can be observed, the habit is not deleterious, for the Styrian peasants live to old age, and no symptoms attributable to the poison have been noted. As a general rule large doses are taken once or twice a week, and no fluid is swallowed for some time afterwards.

It is also stated that large doses can be taken with impunity by animals previously treated with increasing quantities of dry arsenic by the mouth; on the other hand this has not been observed under arsenic given in solution hypodermically, and the statement is made that animals that tolerate large quantities by the mouth are killed by small quantities injected in this way. This has led to the view that in tolerance the intestinal cells fail to absorb the arsenic, and the poison thus does not reach the body cells, which remain susceptible to it. Thus Joachimoglu holds that tolerance is limited to the intestinal cells, which no longer undergo inflammation and necrosis under arsenic. But considerable quantities of arsenic have been found in the urine of arsenic-eaters, showing that absorption occurs. Unfortunately these experiments and observations have not taken account of the great variation in the fatal dose of dry arsenic taken by the mouth; when coarse powder is taken, many times as much arsenic may be taken as when a fine powder is swallowed, and still less is dangerous when a solution is employed. And no tolerance has been definitely shown to be developed when the drug is given in solution; until this has been done, the development of tolerance to arsenic has not been demonstrated; the whole question requires further examination.

As a contrast to the Styrian peasants, the miners of Reichenstein may be mentioned, who are constantly exposed to arsenic owing to its being contained in large quantities in the ore. These people are described by Geyer as short-lived, very subject in adult life to dropsies and respiratory diseases; they offer little resistance to microbial infection, and frequently present the skin and nervous symptoms of arsenic poisoning. The difference in the reactions of these people may arise from the Styrians swallowing the dry crystals, which fail to be dissolved and absorbed, while the ore-workers may be exposed to a finer powder, which may perhaps reach the blood through the lungs. Differences in the general nutrition may also play a part, for Delepine and others have found that animals supplied with abundant food and in good hygienic conditions survive under chronic arsenic poisoning much longer than less well-nourished ones. This difference in the nutrition may also explain the fact that in epidemic poisoning, as in the Manchester cases, comparatively few of the persons exposed to the poison exhibited any symptoms from it.

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Arsenic is **Excreted** very slowly, some appearing in the urine and feces within twenty-four hours, but only about one-fifth of that absorbed being eliminated in this way. The rest is stored in the tissues for a long time and slowly got rid of in the hair and epidermis, in which arsenic may be found for many months after it has disappeared from the urine and feces. Traces may be found in other secretions, and fatal intoxication has been observed in a child from the milk of its mother, who was suffering from acute poisoning. Arsenic is transmitted to the fetus through the placental circulation. In the urine arsenic appears as arsenite and arsenate. It is probable that the effects, especially the paralysis, lasts long after the drug has been excreted, lesions having been induced which only recover slowly.

Arsenic disappears rapidly from the blood when injected, being taken up by the tissues in which it forms firm combinations with the nucleins; it is found chiefly in the liver, and is also deposited in the kidney, in the walls of the stomach and intestine, and in the spleen and lungs. Much smaller quantities are found in the muscles and in the nervous tissues, in which it is said to occur in larger proportion in the white than in the gray matter. It has been detected in the cancellous bones of the skull and vertebræ after it has disappeared from all the other organs.

Arsenic and phosphorus are included in one group in chemistry and their effects on living organisms present sufficient resemblance to justify their association in the pharmacological system. The mucous membranes and the skin are more affected by arsenic, however, and the circulation is more rapidly depressed, while the fatty infiltration is much more prominent in phosphorus poisoning. The differences between their effects are more in degree than in kind, and there seems no question that their ultimate action on protoplasm is of the same nature. It is to be noted, however, that the action of phosphorus is due to the element itself while the oxides of arsenic alone are capable of modifying vital functions. It has been suggested that the toxic action of arsenious acid results from its combining with the sulfhydril compounds of the cell thus inhibiting cellular respiration.

The **Sulfur Compounds** of arsenic are entirely insoluble and are therefore not absorbed as such, but it seems likely that small quantities of arsenious acid are formed from them in the intestine by microbes. Commercial orpiment often contains large amounts of arsenious acid.

Arseniuretted Hydrogen (AsH_3) is an exceedingly poisonous gas, which has caused a number of fatal accidents from being inhaled accidentally in chemical laboratories. Its action is quite different from that of the oxides of arsenic and there is no reason to suppose that arsenites give rise to appreciable amounts of the gas in the body, or that the effects of the latter are due to the formation of arsenites. Its action arises from its great affinity for hemoglobin, which takes it up in large quantity and combines with it or with some product derived from it. This leads to hemolysis, and the liberated hemoglobin induces severe symptoms in the course of its excretion. In the test-tube arseniuretted hydrogen forms a combination with hemoglobin which gives a characteristic spectrum but this has not been shown to occur in living animals. Most of the symptoms appear to arise from the hemolysis, but there may be in addition some direct action on the central nervous system.

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Arseniuretted hydrogen induces intense headache, nausea and vomiting, prostration and fainting fits, cyanosis and collapse. Hemoglobin, methemoglobin, hematin and occasionally blood are passed in the urine, and more rarely the stools contain blood. Sometimes the urine is entirely suppressed from the tubules being plugged with blood cells and débris, and intense icterus appears from the formation of excess of bile-pigment from the hemoglobin of the disintegrated corpuscles. Edema of the lungs or sudden failure of the heart is the cause of death. Some of the gas is excreted by the lungs, and may be recognized by its garlic odor, and some arsenic appears in the urine, but it is not known in what form. It is estimated that one part in 100,000 parts of air is injurious to man if breathed for a few hours.

Therapeutic Uses.—Arsenious acid has been used externally as a *caustic,* formerly in various forms of malignant disease, more recently in lupus, in which it is said to destroy the diseased surface while leaving the healthy skin unaffected. It has been superseded, however, by the introduction of surgical measures and treatment with light rays. Arsenic is also a component of "quack"cancer salves where its corrosive action often leads to widespread ulceration. Arsenious anhydride has also been used in dentistry to destroy the pulp in decayed teeth; this destructive, caustic action proceeds more slowly than under more violent corrosives, so that there is little or no pain from it.

Internally arsenic was formerly used in a variety of disorders including malaria, chorea, neuralgia, chronic rheumatism, asthma, pernicious anemia, erythemia and as a tonic, but its uses in these conditions is irrational.

Many forms of **Skin Disease,** particularly psoriasis, chronic eczema, and *lichen ruber* were also formerly treated with arsenic but its value in these conditions is also questionable. Inorganic arsenic was also formerly used in the treatment of syphilis and trypanosomiasis but has been replaced in these conditions by the more effective organic arsenicals to be described in the next section.

The only important therapeutic use of inorganic arsenic at present is in the treatment of **Chronic Myelocytic Leukemia** in which condition the drug produces a remission comparable to that observed following irradiation (Forkner and Scott). It is sometimes effective when refractoriness to irradiation occurs. It is of little value in chronic lymphocytic leukemia and of no benefit in acute leukemia. In the treatment of chronic myelocytic leukemia, 0.3 cc. (5 minims) of Fowler's solution (potassium arsenite) is given three times daily for two days in water or fruit juice immediately after or with meals. The dose is increased by 0.05 cc. (a minim) every other day until 0.6 cc. (10 minims) are being taken three times daily. Thereafter the total daily dose is increased by one minim until the desired response is obtained or toxic symptoms supervene. In the latter case, the medication is omitted for two to five days and then resumed, decreasing the previous maximum dosage by 1 minim each day until a tolerable maintenance dose is established which is continued thereafter.

With continued administration of arsenic, watch must be kept for symptoms of chronic poisoning and, if they arise, the drug must be discontinued at once. The first symptoms are generally diarrhea and

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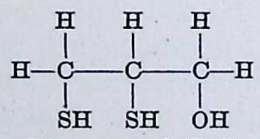
disordered digestion, loss of appetite and discomfort in the stomach region, a feeling of constriction in the throat, and redness and swelling of the conjunctiva and eyelids. An early symptom of neuritis of the motor nerves is disappearance of the ankle-jerk. However, in the treatment of chronic myelocytic leukemia the milder toxic symptoms such as nausea, anorexia and restlessness may be disregarded, for only by uninterrupted treatment are the best results obtainable.

In Acute Arsenic Poisoning the stomach ought to be emptied at once by means of the stomach tube or by an emetic (apomorphine). The stomach washing is to be continued for some time, as arsenic is very insoluble. Iron or magnesium preparations have been advised in order to form a loose chemical combination with the arsenic; a reputed antidote is freshly precipitated iron hydrate formed by adding magnesia to a solution of iron sulfate. Experiments on animals throw doubt on the value of these antidotes and reliance is to be placed mainly on repeated and copious lavage. In acute poisoning general symptomatic measures are indicated.

The collapse is treated by the ordinary measures used in shock. In chronic poisoning the paralysis is treated by stimulating the muscles with the galvanic current; the other symptoms, by suitable general treatment. The use of sodium thiosulfate is of questionable value (Muir *et al.*).

During the recent war a search for antidotes effective in neutralizing the actions of arsenical vesicants led to the discovery of **Dimercaprol**, or British Anti-Lewisite (**Bal**). This compound which chemically is



Dimercaprol (Bal)

2, 3-dimercaptopropanol, exerts its antidotal action by forming a less dissociable complex with arsenic than is formed with natural cellular constituents. It has been found to be effective in the hemorrhagic encephalitis, fever, dermatitis and other toxic manifestations following arsenical therapy. Dimercaprol has also been used in patients with acute mercury poisoning. In severe cases of arsenic poisoning a dose of 3 mg. of dimercaprol per kilogram of body weight is given intramuscularly every four hours for two days, four injections on the third day and twice daily thereafter for ten days or until recovery. It is injected intramuscularly in the form of a 10 per cent solution in peanut oil. In acute mercury poisoning larger doses are indicated.

Preparations

Arseni Trioxidum (U. S. P., B. P.), Acidum Arseniosum (As_2O_3), arsenous, or arsenious, acid anhydride, white arsenic, ratsbane, forms a white powder, or opaque, porcelain-like masses, or a transparent, amorphous surface like glass. It dissolves slowly in cold water, the glassy variety requiring about 30, the porcelain about 80, parts of water. It is almost tasteless and has no odor. Dose, 0.002 gram; B. P., 0.001 to 0.005 gram.

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LIQUOR ACIDI ARSENOSI (U. S. P.), a 1 per cent solution of arsenious anhydride acidulated with hydrochloric acid. Dose, 0.2 cc.

LIQUOR ARSENI ET HYDRARGYRI IODIDI (B. P.), Donovan's solution, contains 1 per cent of arsenic iodide and 1 per cent of red mercuric iodide. This solution is clear and yellowish, without odor, but with a harsh metallic taste. Dose, 0.3 to 1 mil.

LIQUOR ARSENICALIS (B. P.), Fowler's solution, a 1 per cent, colorless, neutral solution of arsenic trioxide. Dose, 0.12 to 0.5 mil.

LIQUOR POTASSII ARSENITIS (U. S. P.), Fowler's solution, contains 1 per cent of arsenious anhydride rendered alkaline with bicarbonate of potash. Dose, 0.2 cc.

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IV. ORGANIC ARSENIC COMBINATIONS

A number of organic arsenic compounds have been introduced into medicine for the treatment of protozoan infections including syphilis and other treponematoses, trypanosomiasis and spirillosis. These drugs constituted the most effective means of treatment until the advent of penicillin. Several years will be required before the status of penicillin in the treatment of syphilis will be entirely established but preliminary results indicate that the relatively non-toxic antibiotic may to a large extent, if not entirely, displace the arsenicals either as the sole drug to be employed or at least as an adjuvant form of therapy.

The organic arsenicals may be classified into two general groups: (1) those in which arsenic is present in the trivalent form (arsphenamine and its derivatives, mapharsen, etc.) and (2) those in which it is pentavalent (tryparsamide, acetarsone, carbarsone, treparsole, etc.). As first claimed by Ehrlich, it is only the former which are treponemacidal, and these are principally used in the treatment of syphilis. Tryparsamide, a pentavalent compound, is used in treating resistant central nervous system syphilis but the pentavalent compounds generally are used chiefly in the treatment of trypanosomiasis, amebiasis and spirillosis.

Toxic reactions and even fatalities may follow the injection of the organic arsenicals. Arsphenamine and its related preparations which are used intravenously are controlled by the *Federal Regulations* cover-

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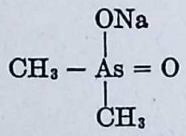
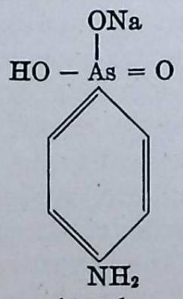
ing serums, viruses and analogous products and are issued only with the approval of the National Institute of Health. A failure to observe the detailed instructions for their preparation and injection may lead to toxic reactions. In addition the first injection of a treponemacidal drug often leads to the so-called **Herxheimer** reaction in which there is a rise of temperature, headache, nausea, malaise, etc. This reaction is attributed to the liberation in the tissue of the foreign protein set free by the destruction of the parasites. Other more serious reactions—gastritis, pruritis, dermatitis, conjunctivitis, jaundice, purpura, anemia, encephalitis, etc., must also be watched for as indicative of more serious toxicity. Also in individuals with severe affections of the circulatory system, or kidneys and other degenerative processes, the arsenicals should not be used.

Inorganic arsenic had some reputation in the treatment of syphilis, being used along with mercury in the well-known Donovan's solution. **Sodium Cacodylate,** the earliest of the organic arsenic compounds to be used in medicine was found to be valueless in the treatment of syphilis but was used as a substitute for inorganic arsenic in anemia and other conditions in which the latter was used.



Sodium cacodylate

When the sleeping sickness of Africa was found to arise from trypanosomes, another protozoan parasite, inorganic arsenic was used to treat it. The results were disappointing, as the quantity of arsenic that could be given was limited owing to its poisonous action on the patient. For inorganic arsenic proved to have little specific affinity for the parasite; in Ehrlich's phraseology, it was not parasitotropic, while it was very poisonous to the tissues of the host, or strongly organotropic. In the test-tube inorganic arsenic preparations are very poisonous to trypanosomes, and they would doubtless be equally destructive in the tissues if they could be applied there without injuring the host.



Atoxyl

Some organic preparations of arsenic proved available for treatment, the first being *Atoxyl,* or sodium arsanilate. Although receiving its name in allusion to its supposed lack of toxicity, atoxyl proved too toxic for therapeutic use. Later the acetyl derivative of atoxyl was found more active in combating trypanosome infections. These combinations

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proved useful in syphilis also, but while destroying the parasites in these diseases, they were not devoid of deleterious action in man. Ehrlich soon pointed out that atoxyl has practically no action on trypanosomes in test-tube experiments and only gains its parasiticidal action in the tissues. He explained this by the view that the pentavalent arsenic compounds, such as atoxyl and arsenic acid, are really inactive in themselves and only acquire activity when they are changed to the trivalent arsenic, such as exists in arsenites. This led him to seek for organic compounds in which the arsenic is trivalent, and the discovery of *Arsphenamine* and *Neoarsphenamine*. Both of these organic compounds are much less poisonous to man and the higher animals than inorganic arsenic, while they maintain the poisonous action toward the protozoa that infest the blood and tissues. In other words they are less organotropic and more parasitotropic. Ehrlich supposed that certain parts of the molecule in these compounds attach themselves to the parasites, and that these haptophoric groups then allow the poisonous part, or toxophoric groups, to act on the protozoa. The tissues of the mammals do not afford points of attachment for the haptophoric groups and therefore are not attacked by the toxophoric radical. This hypothesis of Ehrlich served a valuable purpose in stimulating and directing research on chemotherapy but new facts have come to light which render it untenable in its original form.

Arsenicals Used in the Treatment of Syphilis

Since Ehrlich's introduction of arsphenamine for the treatment of syphilis a number of organic arsenic compounds have been prepared and used in the treatment of this common disease. Until the recent advent of penicillin these organic arsenicals were the principal drugs effective in the treatment of syphilis. Whether or not this antibiotic shall ultimately displace the arsenic derivatives or offer an adjuvant method for therapy, must await further experimental study. The organic arsenicals used in antiluetic therapy may be classified as (1) those derived from arsphenamine base which contains two benzene rings and (2) those containing a single benzene ring.

The mechanism of action of the organic arsenicals has been a matter of much investigation. Voegtlin and Smith found that compounds of the type of R–As=O ("arsenoxide") produce a rapid trypanocidal action both *in vivo* and *in vitro*, and also produce more immediate toxic effects on the host. They suggest that arsphenamine undergoes partial oxidation in the body and that these oxidation compounds are responsible for the curative and toxic actions of arsphenamine. Voegtlin also found that arsenoxide combines readily with substances containing a sulfhydryl grouping and the latter can inactivate the former. He suggests that combination with sulfhydryl compounds, glutathione for example, may play an important part in explaining the toxic and curative action of arsenical derivatives. Eagle, working with virulent *S. pallida* fresh from rabbit chancres, found that arsphenamine and neoarsphenamine are antispirochetal *in vitro* in concentrations of

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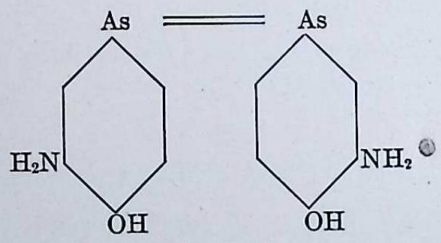
about 1 in 200,000 and arsenoxide in a concentration of about 1 in 1,000,000. The organisms were immobilized and rendered non-infectious for other rabbits. These concentrations are of the same order as those attained *in vivo* after therapeutic administration. The idea originally held that compounds of the arsphenamine type are inactive outside the body is therefore no longer tenable, though it is still probable that they are converted in the body into some more active compound.

All these experiments suggest that the actions of arsphenamine and of its congeners do not admit of so simple an explanation as Ehrlich proposed and that coöperation of the tissues of the host is needed before the therapeutic virtues of these compounds are fully displayed. In the tissues they are changed into some more highly active organic compound of arsenic.

Derivatives of Arsphenamine Base

Arsphenamine, the 606th compound investigated by Ehrlich was introduced by him in 1907. It is *para* dihydroxy-*meta*-diamino arsenobenzene and was introduced under the name "salvarsan," but is also known as Ehrlich's 606, diarsenol or arsenobenzol.



Arsphenamine

Arsphenamine is a specific remedy for syphilis in all its stages. It is injected intravenously in doses of 0.2 to 0.4 grams being prepared by a special technique in the form of the disodium salt prior to injection.

In the treatment of early syphilis arsphenamine is given in courses of one injection weekly for six to eight weeks alternately with a course of heavy metal therapy. This is continued for a year or more after all lesions are healed and the Wassermann reaction is negative.

When arsphenamine is injected intravenously, there are as a general rule no symptoms elicited, but in individual cases effects varying from comparatively trivial disturbances to grave and even fatal issues have been met with. Some of the more serious effects are definitely a variety of arsenical poisoning; others, less severe, are due to the bulk of fluid injected and the colloidal nature of the solution.

Immediately after the injection there may be a feeling of faintness, headache, flushing and heat in the head and face, giddiness and nausea, general malaise, profuse sweating, dyspnea, or restlessness and tremor; vomiting and diarrhea have occurred sometimes. There may be a fall in blood-pressure. Some fever followed in the earlier cases, from the use of water contaminated with the proteins of killed bacteria. These early symptoms are rarely of serious import, and have become rarer, as experience in the use of the drug has grown and suitable precautions have been taken to prepare the patient for what should be regarded as in the nature of a surgical operation. The faintness and syncope are sometimes due to fear of the injection and are rarely seen if the patient is in the recumbent position.

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More alarming effects which are of the same nature as the flushing are the so-called "anaphylactoid" symptoms, marked by swelling of the lips and tongue, cyanosis and severe dyspnea, urticarial and other skin eruptions, herpes labialis, stomatitis and albuminuria. When these symptoms arise in the later stages of a course of treatment, they suggest caution in the dosage and longer intervals between the injections. These effects seem due not to a toxic action of arsenic but to an alteration in the blood proteins, or perhaps agglutination of the red blood corpuscles, resulting from the colloidal nature of the arsphenamine injection. They do not occur after intramuscular injections. These reactions can generally be arrested by an intramuscular injection of epinephrine or prevented by previous administration of ephedrine by mouth.

Not infrequently swelling and edema occur around the local manifestations of syphilis after arsphenamine has been injected; for example, when arsphenamine is administered in syphilitic skin eruptions, the skin lesions swell up, and the secretion from ulcers is increased (Herxheimer). This may perhaps arise from the poisonous action of the proteins freed from the dead spirochetes.

Severe symptoms have arisen in rare cases several days after the injection, and fatalities have followed either from cerebral symptoms (encephalitis hemorrhagica) culminating in convulsions, coma and death, or from skin affections (dermatitis exfoliata), or from jaundice developing into acute yellow atrophy of the liver. These fatalities have become rarer in recent years and toxic effects of this nature are a variety of arsenical poisoning.

Toxic effects from arsphenamine may be due to impurity of the drug itself but misadventures from this cause have become less common since biological standardization of it has been adopted. The possibility of faulty technique, however, remains. Scrupulous attention is needed to every detail of administration and the solution must be freshly prepared and correctly neutralized. Even when all precautions are taken, however, a small number of cases remain in which arsphenamine produces unusually toxic effects that can only be ascribed in the meantime to idiosyncrasy of the patient. Fortunately the number of accidents with arsphenamine is small in comparison with the frequency of its use.

Excretion.—When a single dose is injected intravenously, arsphenamine appears unchanged in the urine in five to ten minutes and persists in this form for five to six hours; thereafter arsenic is found in the urine for some days, apparently in the form of arsenites and arsenates. It is excreted in the stools in larger proportions than in the urine, and the bile contains large amounts. It disappears from the blood at about the same time as from the excretions, but may be found in the liver, spleen, bone-marrow and kidney rather later; an arsenic reaction may be obtained from the liver and marrow as late as ten days after the intravenous injection in animals, but no arsenic is to be found in any of the organs after fifteen days.

It would thus appear that after its intravenous injection most of the arsphenamine disappears from the blood in a few minutes, though small amounts remain there for several hours. Some arsphenamine may be excreted in the urine unchanged, but after some hours inorganic arsenic compounds take its place and are excreted in the urine and feces. The total excretion is slow and some appears to be stored in the liver and other organs, from which it is gradually released into the blood. Arsenic is not found in the cerebrospinal fluid after the intravenous injection of arsphenamine.

The excretion of neoarsphenamine resembles that of arsphenamine, but is more rapid. Pentavalent compounds, like atoxyl or tryparsamide, are much more rapidly excreted, probably because they are not fixed to the same extent by the tissue cells.

Therapeutic Uses.—Arsphenamine was introduced by Ehrlich for the treatment of *syphilis* and has been succeeded in large part by other arsenicals which have the advantage of being available with less manipulation. At first it was hoped that a single injection of arsphenamine would suffice to destroy the spirochetes of syphilis and realize the ideal

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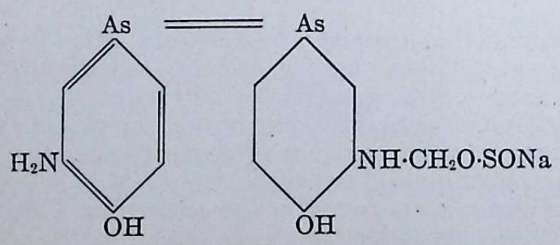
of complete sterilization of the tissues as far as the agent of this disease was concerned. Although this hope has not been entirely fulfilled, the introduction of these arsenical compounds in the treatment of syphilis was a very important advance in medicine. Very frequently a single injection of arsphenamine frees the blood and local lesions from parasites within a few hours, and the Wassermann reaction, which is specific for syphilis, disappears; in a certain number of early cases the disease is healed, but in others the reaction returns. Some weeks or months later the spirochetes can be found again and symptoms of secondary syphilis begin to appear. The first injection suffices to destroy the great mass of parasites, but a few survive and reinfect the tissues. In practice it is found that repeated injections are necessary. Voegtlin found that in rabbit syphilis, 4 doses of 6 mg. per kilo at intervals of six days gave better results than 24 mg. per kilo in a single dose and concluded that the effectiveness of repeated fractional doses is due to the prolonged contact of the drug with the tissues.

In the treatment of several other protozoal diseases, arsphenamine has proved as successful as in that of syphilis. Thus in *frambesia* (yaws), *recurrent fever*, and *Vincent's angina*, it is remarkably efficient, and in *spirillosis* of the lower animals an equal success has followed its use. However, as in the case of syphilis, penicillin shows promise of becoming the drug of choice in these diseases.

In cases of emaciation and malnutrition, the organic arsenic preparations are to be used with special care and in low doses, and in disease of the heart, vessels, or brain, and in very old and feeble persons or those suffering from nephritis or diabetes, arsphenamine should not be employed.

Neoarsphenamine, was introduced by Ehrlich as a substitute for arsphenamine which did not require alkalinization prior to injection. It is also known as neosalvarsan, Ehrlich 914, neodiarsenol and novarsenobenzol. Chemically it is the sodium methanal sulfoxylate derivative of arsphenamine.



Neoarsphenamine

Neoarsphenamine is less toxic than arsphenamine and is therefore used in larger doses (0.3 to 0.5 grams) and may be given intramuscularly or intravenously, the latter route being preferred. Neoarsphenamine has the advantage over arsphenamine in that it is easier to prepare and administer; causes fewer gastro-intestinal reactions; and is less irritant. It is an unstable compound and may deteriorate unless properly preserved.

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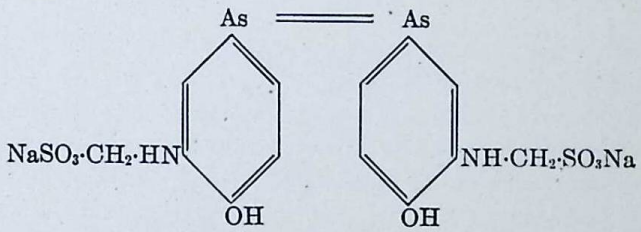
Silver Arsphenamine, is believed to be a double salt of disodium arsphenamine and silver oxide but its exact molecular formula has not been established. It was introduced as an improvement over arsphenamine with a view of combining the antisyphilitic action of silver with that of arsphenamine. The same untoward reactions may follow its use as are observed with arsphenamine and neoarsphenamine. It is administered intravenously in doses beginning with 0.1 gram and increasing gradually at intervals of not less than four days to 0.2 gram as a maximum in women and 0.3 gram in men. Smaller initial doses are indicated in patients with nervous system disorders.

Sulfarsphenamine, the disodium dimethylenesulfonate of arsphenamine differs from neoarsphenamine in having two side chains instead of one and an extra oxygen atom on the sulfur. It is more stable in solution in the presence of air than neoarsphenamine but is more apt to give late reactions and dermatitis, purpura, meningo-vascular reactions and aplastic anemia. It is administered intramuscularly in doses not exceeding 0.4 to 0.5 gram. Since it is well tolerated by intramuscular injection, it is useful in cases in which intravenous injection is difficult as in the obese or in infants.



Sulfarsphenamine

Bismarsen is a sodium salt of a bismuth derivative of arsphenamine methylene sulfonic acid introduced to combine the chemotherapeutic effects of arsenic and bismuth in a single compound. It is administered intramuscularly in an initial dose of 0.1 gram with succeeding doses of 0.2 gram, weekly at first and then bi-weekly in courses of treatment of 20 doses or more. Bismarsen is less effective than the other arsphenamines and is slower in bringing about healing of the lesions and reversing the Wassermann reaction.

ORGANIC ARSENICALS CONTAINING ONE BENZENE RING

Oxophenarsine Hydrochloride is commonly referred to by its tradename, mapharsen, which is derived from the first letters of its chemical designation, *meta*-amino-phenyl-hydroxy-arsine-hydrochloride. This compound was originally investigated by Ehrlich and Hata but discarded as too toxic. Tatum showed, however, that despite its toxicity in comparison with arsphenamine, the compound was therapeutically highly effective and hence of value in syphilotherapy. It has the advantage of being a pure stable chemical substance and relatively easy to administer, and in the doses used in therapy, well tolerated. It is administered intravenously in doses of 0.03 (for women) and 0.04

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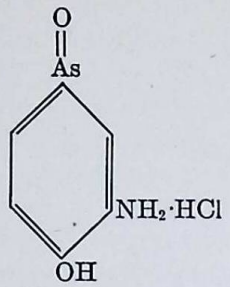
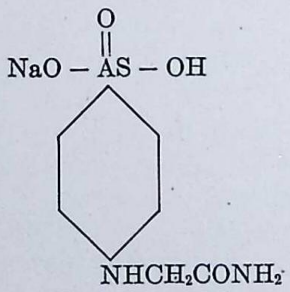
(for men) grams initially and 0.04 (for women) and 0.06 (for men) grams thereafter every four or five days.



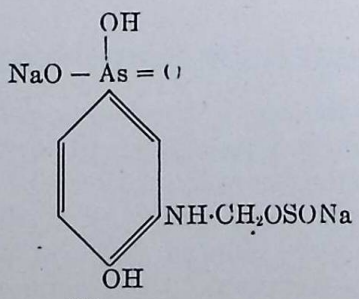
Mapharsen

Tryparsamide, the sodium salt of phenylglycineamide-4-arsonic acid, was originally introduced for the treatment of trypanosomiasis due to *T. gambiense* but is also used in resistant cases of syphilis of the central nervous system, particularly in patients with early dementia paralytica. It is less effective in tabes and is of no value in other forms of syphilis. It is used extensively in central nervous system syphilis.



Tryparsamide

Like other pentavalent arsenic compounds particularly those in which an $-NH_2$ group is in the position *para* to the As, tryparsamide has a tendency to produce amblyopia as well as nitroid reactions. The visual injuries should be guarded against by frequent examination of the eye grounds and visual fields. Tryparsamide is administered intravenously in doses not exceeding 0.04 to 0.05 gram per kilogram of body weight not oftener than once a week.



Aldarsone

Phenarsone Sulfoxylate (aldarsone), sodium aminohydroxyphenylarsonate methanal sulfoxylate, is a pentavalent arsenic derivative which is used in the treatment of **Trichomonas Vaginitis** (by insufflation locally) and central nervous system syphilis. For the treatment of central nervous system syphilis 1 gram of the drug, dissolved in 10 cc. of water,

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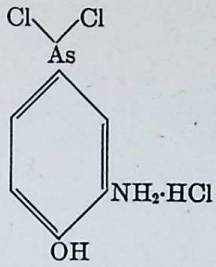
is injected intravenously weekly for forty to fifty weeks with concurrent bismuth therapy during a portion of this time. It is also used as a supplement to fever therapy.



Clorarsen

Dichlorophenarsine Hydrochloride, (clorarsen) was discovered many years ago but only recently shown to be useful in the treatment of syphilis. It must be properly buffered prior to injection and is administered in initial doses of 0.03 gram (for women) and 0.04 gram (for men) intravenously every four or five days, the dose being increased to 0.04 gram (for women) and 0.068 gram (for men) beginning with the second injection.

Acetarsone, (Stovarsol) a pentavalent arsenic compound, was originally introduced for oral use in the prophylaxis and treatment of syphilis but its action in this disease is uncertain and it is used primarily in the treatment of amebiasis in connection with which it is therefore discussed. Acetarsone is also used in the treatment of *Trichomonas vaginitis* and has been highly recommended for the treatment of yaws. In *Trichomonas vaginitis* it is applied locally in the vagina in the form of a powder. **Carbarsone,** another pentavalent arsenic compound is also used in amebiasis.

Fever Therapy.—Mention may be made here of the treatment of general paralysis by artificial inoculation with the *Plasmodium malariæ,* either from infected blood or from the mosquito. This method of treatment was introduced by von Jauregg in 1917, since when it has been extensively tried in most countries. The attack of benign tertian malaria thus produced is allowed to run its course for about 6 to 10 rigors, when it is stopped with quinine. In some cases the patient has been allowed to have relapses of malaria according to the effect produced on the paretic symptoms. The malaria is then permanently stopped by quinine medication. In about 25 per cent of the cases marked amelioration of the original symptoms occurs. Malaria seems to act as a kind of "shock" therapy, which is partly due to the fever induced. Other forms of fever, artificially produced, have been tried in neurosyphilis with beneficial effects.

DRUGS USED IN TRYPANOSOMIASIS

Following the World War I the German dye trust marketed a secret remedy called Germanin or Bayer 205 which was claimed to be effective against African sleeping sickness and the use of which it was hoped would open up vast areas of Africa to immigration. Fourneau, soon elucidated the structure of Bayer 205, synthesized it and made it available as Fourneau 309. The drug was remarkable in the fact that it contained

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no metal and thus proved that non-metallic organic compounds might be effective as anti-infective chemotherapeutic agents. The use of Fourneau 309 has proved disappointing in African sleeping sickness, being effective only in the early hemic cases of infection with *T. rhodesiense* and of little value in the more common infection with *T. gambiense*. In the latter disease, tryparsamide, which has already been discussed under the antisyphilitic drugs has proved much more effective. Germanin, or Fourneau 309 is included in the British Pharmacopeia under the official designation **Suramin.**

In addition to tryparsamide, several other arsenicals have been tried in African trypanosomiasis. The drugs most recently suggested are **Triazine Arsonic** acid, introduced by Friedheim, *p*-arsenosophenyl butyric acid and various diamidine derivatives (stilbamidine, pentamidine, etc.)

The treatment of trypanosome infections with arsenic preparations is complicated by the fact that the parasites rapidly develop *tolerance* to the drug. If an animal infected with trypanosomes receives an injection of atoxyl, the parasites disappear from the blood and none may be found in it for many days or weeks; then a few reappear and rapidly multiply but are again destroyed by a second dose; the interval before they are again seen in the blood is shorter, and becomes shorter with each succeeding injection until atoxyl no longer frees the blood from trypanosomes even in the maximal dose which can be given without injury to the host. If a second animal is now infected with the blood of the first containing these resistant trypanosomes, it is not improved by atoxyl, the descendants of the resistant type maintaining their tolerance of atoxyl through an indefinite series of generations. This form of resistance appears to arise, partly at least, from a process of selection by the survival of the most tolerant. The first dose of atoxyl destroys all but the most resistant of the trypanosomes, and these multiply and again the most resistant survive the second dose, and thus a strain is eventually reached which is as resistant to the atoxyl as the tissues of the host. This change in the character of the trypanosomes depends on their asexual generation and is readily intelligible when it is realized that successive generations are really only fragments of the original resistant individuals. Whenever a sexual cycle is interposed, all the resistance to atoxyl is lost. A strain of trypanosomes which has developed tolerance for one of the organic arsenical preparations (arsenic-fast) is generally tolerant to the others also, but not in such high degree to inorganic arsenic.

Preparations

Acetarsol (B. P.), arcetarsone, 3-acetylamino-4-hydroxyphenylarsonic acid. Dose, 0.06 to 0.25 gram.

Arsphenamina (U. S. P.), Arsphenamine, Salvarsan, diamino-dihydroxyarsenobenzene hydrochloride, $HClNH_2OHC_6H_3As=AsC_6H_3OHNH_2HCl.2H_2O$, is a yellow, crystalline powder containing 31.5 per cent of arsenic metal and readily oxidizing in the air; it is accordingly kept in vacuum tubes. It is readily soluble in water with an acid reaction. Dose, 0.3 to 0.6 gram by intravenous injection. The arsphenamine tube should not be opened until required. The contents are dissolved in sterilized saline (0.9 per cent) and neutralized to litmus with normal caustic soda solution (0.85 cc. of normal NaOH is required for each 0.1 gram of arsphenamine); a precipitate is formed which redissolves on shaking. The solution should be very dilute for intravenous injection, at least 25 cc. being used for each 0.1 gram arsphenamine. Great care must be taken that the solution is not injected into the tissues around the vein as it causes intense pain and induration.

Neoarsphenamina (U. S. P., B. P.), Neosalvarsan, is a yellow crystalline powder, containing about 20 per cent of arsenic. Three parts of neoarsphenamine therefore equal in arsenic content about 2 parts of arsphenamine. Dose, intra-

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venously, U. S. P., 0.45 gram; B. P., 0.15 to 0.9 gram. The contents of a newly opened tube are dissolved in 10 to 15 cc. of sterile, recently distilled water. The solution is neutral in reaction and requires no addition of alkali as in the case of arsphenamine.

SULFARSPHENAMINA (U. S. P.), SULPHARSPHENAMINA (B. P.), an orange-yellow powder, readily soluble in water, yielding an acid solution. For intramuscular or subcutaneous use it is dissolved in freshly-prepared distilled water in the proportion of about 0.1 gram to 0.3 cc.; for intravenous use in the proportion of 0.1 gram to 3 cc. Dose by subcutaneous or intramuscular injection, U. S. P., 0.45 gram; B. P., 0.1 to 0.6 gram.

TRYPARSAMIDUM (U. S. P., B. P.), a white crystalline powder containing about 25 per cent of arsenic. Dose, 2 grams dissolved in 10 cc. distilled water, intravenously; also given intramuscularly.

DICHLOROPHENARSINÆ HYDROCHLORIDUM (U. S. P.), a white powder, soluble in water, distributed usually as a mixture with buffering agents. Dose, 45 mg., intravenously.

OXOPHENARSINÆ HYDROCHLORIDUM (U. S. P.), a white powder, soluble in water, distributed usually as a mixture with buffering agents. Dose, 45 mg., intravenously.

SURAMINUM (B. P.), suramin, $C_{51}H_{34}O_{23}N_6S_6Na_6$, the symmetrical urea of the sodium salt of *m*-benzoyl-*m*-amino-*p*-methylbenzoyl-l-aminonaphthalene-4:6:8-trisulphonic acid. Dose, intravenously, 1 to 3 grams.

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V. PHOSPHORUS

In the early part of the last century phosphorus was regarded almost as a panacea in therapeutics, but it has been discarded as without therapeutic value whatever. At the same time, it has been the subject of much and laborious investigation, partly because formerly it frequently gave rise to poisoning, and partly because the study of its effects has thrown much light on some physiological and pathological processes. A more detailed account of these effects was given in previous editions of this book. Phosphorus seems to be of diminishing therapeutic and toxicological importance, so that only a brief survey of its actions is now necessary.

Phosphorus is absorbed with difficulty, because it is very insoluble in water and the body fluids and is only slowly volatilized at ordinary body temperature. Large masses of phosphorus may thus pass through

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the alimentary canal without serious effects, because they fail to be dissolved and absorbed. But when it is taken in a finely divided condition or in solution in oil, it gives rise to symptoms in very small quantity, and has been found to induce fatal poisoning in man in doses of 0.05 to 0.1 gram. The red amorphous phosphorus is much less poisonous than the ordinary yellow form because it is less soluble and also less volatile, and consequently fails to be absorbed.

Phosphorus has often been used as a suicidal poison, generally in the form of rat poison or match heads. Formerly each match head was estimated to contain 3 to 5 mg. of phosphorus, so that 15 to 20 match heads might induce fatal poisoning. The use of poisonous yellow phosphorus in match manufacture is now generally prohibited by law. Phosphorus sesquisulfide (P_2S_3), now usually employed, seems to be even safer than red phosphorus. "Safety matches" have no phosphorus on the sticks, only red phosphorus on the striking surface.

Symptoms.—When a poisonous dose of phosphorus is swallowed, no effects are elicited, as a general rule, for several hours. The first symptoms are pain and discomfort in the region of the stomach, nausea and eructation of the vapor with its characteristic garlic odor, and then vomiting, the contents of the stomach having the same odor, and being phosphorescent in the dark. Later, bile may be vomited, and some diarrhea may set in, although this is not a common symptom. The nausea and vomiting often continue without further symptoms for several days, but frequently disappear, and the patient apparently recovers, particularly if the dose has been small, or if most of it has been removed by vomiting or by washing out the stomach. In the course of a few days, however, the symptoms recur, and are generally accompanied by some jaundice; the pain extends from the stomach to the liver, and soon to the whole of the abdomen. The vomited matter no longer contains phosphorus, but may be bloody. The patient complains of general weakness and faintness; the pulse is weak, the liver extends far below the ribs, and the urine shows characteristic changes (see page 189); hemorrhages occur from the nose, bowel, uterus and under the skin, and eventually a condition of collapse and fatal coma or delirium and convulsions follow.

Exposure to the fumes of phosphorus has long been known to give rise to periostitis and necrosis of the lower jaw. The disease begins from a carious tooth or from some lesion of the gum, and may involve most of the jaw, which becomes swollen and painful and eventually evacuates large quantities of pus with pieces of dead bone. This necrosis was formerly frequent in match factories, but has become almost only of historical interest since amorphous phosphorus has been substituted for the yellow form, and since greater attention has been paid to the ventilation of the factories and to the condition of the teeth of the employees.

Action : Fatty Infiltration.—A very striking feature in phosphorus poisoning is the appearance of numerous fat globules in the cells of many organs, notably in those of the liver, kidney, gastric and intestinal glands, and in the muscle fibers of the heart, stomach, intestine, smaller arteries, and often of the skeletal muscles. This fat is ordinary fat transported from the positions which it normally occupies and deposited in the cells of the liver, heart, and other organs. The process commences in cloudy swelling of the cells, followed by the appearance of granules which soon develop into fat globules. Eventually the degenerated cells break up into detritus.

Another feature in phosphorus poisoning, which is, however, better seen after repeated small doses than after a single large one, is the **Proliferation of the Interstitial Connective Tissue** of the stomach, liver and kidney, which finally induces typical cirrhosis of these organs; it appears to be a secondary result of the necrosis of the parenchyma cells, and may result in dropsy, anemia, and cachexia in animals.

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The fatty changes in the glandular cells of the **Stomach** and **Intestine** explain the abdominal pain, the vomiting and the occasional diarrhea seen among the secondary symptoms. The earlier phases of this action may be the cause of the vomiting and nausea of the first stage.

The **Liver** is early involved in the action of phosphorus. There is a rapid disappearance of the glycogen of the liver in phosphorus poisoning; this is said to precede the other changes in the liver cells.

The fatty changes in the liver cause a considerable increase in the area of hepatic dulness, and at the same time induce some pain and tenderness over the organ.

FIG. 7.—Section of the head of the femur in a calf. *A*, normal; *B*, after treatment with minute doses of phosphorus; *C*, the cap of dense bone at the growing point. (After Wegner.)

In the **Kidney**, the fatty degeneration of the epithelium may account for the albuminuria, which is not generally severe, and is not infrequently absent in cases of poisoning. Fatty casts and even globules of fat are often found in the urine in cases which run a chronic course. Blood and hemoglobin may also appear in it from hemorrhages into the kidney. The urine is normal in quantity in the early stages of the intoxication, but afterward becomes deficient, and towards death complete anuria may be observed. When icterus is present, the urine may be dark in color from the bile pigment excreted, and bile acids are also often contained in it.

The **Fate** of phosphorus in the body is still obscure. It is possible that some of it is oxidized to phosphoric acid, and some phosphorus is said to be excreted by the lungs, although the statement that the breath becomes phosphorescent seems to be extremely improbable. It is also excreted in the urine in some organic combinations, of which nothing is known, though they are said to be volatile. In pregnant animals poisoned with phosphorus the fetus is found to undergo fatty degeneration, so that the poison would seem to pass through the placenta. Phosphorus injected hypodermically acts much slower than when swallowed.

Phosphuretted hydrogen (PH_3) induces the same symptoms as phosphorus, when it is given in repeated small quantities. Large doses are very rapidly fatal, and the symptoms differ entirely from those of phosphorus poisoning, consisting of marked dyspnea, purgation, weakness, tremor, and finally violent convulsions and respiratory failure. The oxygen compounds do not seem to have any such effects, and for the most part are harmless except in very large doses.

Treatment of Phosphorus Poisoning.—Phosphorus is comparatively slowly absorbed from the alimentary canal, so that in the early stages an attempt ought to be made to remove it by emetics or the stomach

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tube, and by purges. Fats and oils must be avoided, as they tend to dissolve the poison and promote its absorption. Phosphorus has been found in the stools three days after its ingestion, and a sharp purge may therefore be of use up to this time.

Sulfate of copper is recommended in phosphorus poisoning, a large dose being given first as an emetic, and afterward smaller doses to form an insoluble compound, copper phosphide. To minimize damage to the liver a high protein, high carbohydrate, low fat diet should be given and the fluid intake maintained at 3 to 4 liters per day.

Therapeutic Use.—Phosphorus was formerly often prescribed but there is no rationale for its use. Radioactive phosphorus in the form of the phosphate is used experimentally in the treatment of certain forms of leukemia in which its effects resemble those of *x*-ray irradiation. It is also a useful tool in elucidating the many biochemical reactions in which phosphate ion is concerned, in the determination of the blood volume, and has been advocated for the treatment of polycythemia.

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PART II

Substances Which Are Characterized Chiefly By Their Local Action

THIS class contains a very considerable number of drugs many of which, however, have practically identical effects and might be discarded without loss to therapeutic practice. Many of its members are irritants, and these have been subdivided for convenience into groups according to the organs on which they exert their chief action and the purposes for which they are used in therapeutics, as gastric, intestinal, or cutaneous irritants. Others act as protectives, covering injured surfaces (demulcents, emollients) and still others precipitate the proteins on the surfaces to which they are applied (astringents). As more specifics have been added to the physician's armamentarium the tendency has been to rely less on these minor drugs which have gradually lost their former importance in Pharmacology. Nevertheless they do often contribute to the comfort of the patient and to the art of medical practice and hence are worthy of attention.

I. SKIN AND MUCOUS MEMBRANOUS PROTECTIVES

1. **Demulcents.**—A large number of colloid substances—chiefly gums, dextrins, certain sugars and starches—owe their use in medicine, not to any changes they produce in the cells with which they come in contact, but to the fact that they are cohesive and serve to protect surfaces mechanically. When they are applied to a sensitive surface, they retard the movement of fluid or air against it and thus preserve it from the effects of these agents. This may be illustrated by familiar examples in which the taste of food is altered by their presence, although they have often no taste or odor in themselves. Sugar dissolved in mucilage tastes less sweet than in water, and acids are also less appreciated, as may be observed in many fruits. For example, the raspberry contains more acid and less sugar than the currant, but in the former the acid taste is concealed by the presence of large quantities of colloids, so that the raspberry is regarded as a sweet fruit, the currant as an acid one. Even cold is felt less when a colloid substance is present in the fluid swallowed; thus, ice-cream or iced milk does not feel so cold on the tongue and throat as frozen water, because the colloid protein substances form a protecting layer over the surface, and prevent the cold mass from reaching the sensory terminations so freely as it otherwise would. Strong salt solution applied to a motor nerve first stimulates and then slowly paralyzes it, but both of these effects are much less marked if the solu-

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tion be made up with mucilage instead of with water, because the salt does not reach the nerve so readily. In the same way, intense pain is caused in a wound by strong salt solution, but is much less severe if the solution contain colloid material.

When demulcents reach the stomach, they act as protectives in some measure so that the reflexes from the epithelium are less active; and irritants cause less inflammation if they are suspended in demulcents than if they are dissolved in water; at the same time the presence of colloidal unabsorbable bodies may increase the efficiency of purgatives by preventing their absorption in the upper part of the bowel. The digestion of proteins outside the body is retarded by the presence of the demulcents, and probably this is also true of the process in the stomach. Colloid bodies also retard the absorption of fluids from the stomach and bowel, and this leads to a feeling of distention, which is much less marked if the same amount of fluid be swallowed without colloid; for instance, water is absorbed more rapidly than milk.

Demulcents are used to cover inflamed surfaces; in tonsillitis, for example, they may be applied as gargles, or better by sucking lozenges containing them. They are not often applied externally for this purpose, as they are liable to serve as media for the growth of microörganisms. In gastric and intestinal catarrh their use is objectionable for the same reason, their slow absorption leading to decomposition with the formation of irritants, which may do more harm than is counterbalanced by their protective action. Instead of demulcents, some of the oils, such as olive oil, have been recommended as protectives in disease of the stomach and intestine.

In acute irritant poisoning the demulcents are often of great value, as they protect the stomach wall from the effects of the poison. The best remedy in these cases, because the most readily obtainable, is milk or white of eggs.

Demulcents are often given instead of pure water in cases where it is desired to administer large quantities of fluid, as they have more "body" and are more agreeable to the taste. Thus, barley water or some other demulcent may be advised in order to assuage the thirst of fever, or to dilute the urine when it is too concentrated or too acid.

Demulcents are often used as the basis of enemata which are intended to be absorbed, because solutions containing colloids are less irritant and therefore less liable to set up peristalsis than pure water. For this purpose starch solution is generally used.

Some of the gums, notably acacia and tragacanth, are seldom advised as demulcents, but are often prescribed in order to hold in suspension in water such insoluble bodies as resins and oils, or to give cohesion to pills and lozenges.

Gelatine is largely used as a demulcent in the preparation of pastilles for the local application of medicaments to the throat. It is also used to solidify glycerin for use as a suppository, and in similar combination for bougies and pessaries. Pastes of gelatine are also prepared for external application. In the form of soups and jellies it is used as a nutrient, being an easily digestible protein.

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PREPARATIONS

ACACIA (U. S. P., B. P.) (gum arabic), a gummy exudation obtained from Acacia Senegal, consists of the potassium, magnesium and calcium salts of a weakly acid substance, arabin, or arabinic acid ($C_6H_{10}O_5$). It is soluble in equal parts of water, and is used as a demulcent, but more largely as a vehicle for other drugs.

AMYLUM (U. S. P., B. P.), or starch, may be formed into a jelly by boiling in water, and may then be used for the same purpose as the demulcents.

EXTRACTUM GLYCYRRHIZÆ (U. S. P., B. P.). Dose, B. P., 0.6 to 2 grams.

EXTRACTUM GLYCYRRHIZÆ LIQUIDUM (B. P.), an extract of liquorice in chloroform water. Dose, 2 to 4 mil.

EXTRACTUM GLYCYRRHIZÆ PURUM (U. S. P.).

FLUIDEXTRACTUM GLYCYRRHIZÆ (U. S. P.). Dose, 2 cc. (30 min.).

GLYCERITUM AMYLI (U. S. P.), GLYCERINUM AMYLI (B. P.), is a jelly formed by heating starch with water and glycerin.

GLYCYRRHIZA (U. S. P., B. P.), or liquorice-root, the root of Glycyrrhiza glabra (var. glandulifera), is used as a demulcent, and more largely to flavor medicines. It has a pleasant, sweet taste, owing to the presence of Glycyrrhizin, an acid glucoside. Dose, B. P., 1 to 4 grams.

MUCILAGO ACACIÆ (U. S. P.), 35 per cent acacia in distilled water. Dose, 15 cc. (4 fl. dr.). (B. P.), 40 per cent acacia in chloroform water. Dose, 4 to 16 mil. (60 to 240 min.).

MUCILAGO TRAGANCANTHÆ (U. S. P.), 6 per cent Tragacanth with water and glycerin. (B. P.), 1.25 per cent in chloroform water. Dose, 4 to 16 mil. (60 to 240 min.).

PULVIS GLYCYRRHIZÆ COMPOSITUS, compound powder of liquorice, containing senna, liquorice, fennel, sulfur and sucrose. (B. P.), dose, 4 to 8 grams.

TRAGACANTHA (U. S. P., B. P.), a gummy exudation from various species of Astragalus, contains salts of arabin and tragacanthin. Tragacanthin differs from arabin in not dissolving, but merely swelling up into a jelly in water. Tragacanth is used chiefly to suspend heavy powders in water.

Numbers of other substances are used as demulcents in domestic medicine, and are found in different pharmacopeias. Examples of these are sassafras pith (*Sassafras Medulla*), slippery elm (*Ulmus*), marshmallow root (*Althea*), linseed (*Linum*), barley (*Hordeum*), salep, verbascum and quince seeds. Iceland moss is a lichen (*Cetraria islandica*), and contains starch bodies together with acids, which can be removed by soaking in dilute alkaline solutions for some time. Irish moss or Carragheen (*Chondrus*), a seaweed gathered on the coasts of Ireland and Massachusetts, contains a carbohydrate, carrageenin. The decoction forms a jelly when cold.

2. **Emollients and Protectives.**—Emollients are bland, oily substances which are applied to the skin to protect it from irritation, and to render it softer and more elastic; they thus bear the same relation to the skin as the demulcents to the mucous membranes. Their effect in rendering the skin softer and more pliable may be due in part to their penetration into the surface layers, but may also be explained by the slight congestion induced by the rubbing and massage used in their application.

The emollients are chiefly animal and vegetable fats and oils, or paraffin derived from petroleum. The effects of these drugs when applied to the skin are purely local. The emollient preparations are supposed to promote the absorption by the skin of drugs dissolved in them, because they mix readily with the thin layer of oily sebaceous matter which covers it. The active substances dissolved in them therefore come into

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intimate contact with the absorbing cells lining the ducts of the glands, while watery solutions are separated from the living cells by a layer of sebum. Aqueous solutions come into more intimate contact with the cells of the mucous membranes and with the subcutaneous tissues, and are therefore more readily absorbed by these than oily solutions. It has generally been supposed that substances are more easily absorbed from the skin if the vehicle is an animal fat, *e. g.*, lard or lanolin, but Bliss found no difference in absorption of iodine, quinine, etc., whether the ointment base was soft paraffin, lard or lanolin. Macht similarly found that none of the common bases used in ointments (*e. g.*, fixed oils, fats, lanolin or petrolatum) facilitated the absorption through the normal skin of drugs incorporated in them. Volatile substances, especially if soluble in fats, are however, readily absorbed through the skin. Solutions in oil of such antiseptics as carbolic acid are much less powerful than those in water, because carbolic acid being more soluble in oil fails to diffuse into the watery protoplasm of the microbe, for which it has less affinity. But antiseptics which are more soluble in water than in oils are said to be equally active in both solvents.

The emollients are applied as protectives in abrasions, cuts, bruises, chapped hands, burns; they are less often used alone in extensive skin diseases, but are usually prescribed in these as the basis of ointments in which other remedies are incorporated. There is no question that the protection afforded to the part and the exclusion of the air and of germs by the oily emollient plays an important part in the action of these remedies, and it seems probable that in many cases equally good results would follow the application of the emollient without any active ingredient.

The emollient ointments are also applied to wounds and mucous membranes as protectives and also as vehicles for other remedies. Here they have a more lasting effect than watery applications, which are more readily absorbed. Emollients are seldom applied to the mouth because of their unpleasant oily taste, but the eye, nose, urethra, vagina and rectum are often treated with them.

Along with the emollients, or oily protectives, may be mentioned another class of mechanical agents, the Dusting Powders. Any dry, insoluble, fine powder applied to irritated surfaces of the skin, or slight abrasions, will protect these from the air, and from contact with the clothes and other sources of pressure. These powders, at the same time, soak up any secretions, and render the injured spot less liable to bacterial infection, as they form a more or less impermeable crust. Powders used for this purpose should not be absorbed, or, if absorbable, should not induce any toxic effects. Those most commonly employed are the phosphate and carbonate of lime, talc, Kieselguhr, fullers' earth and kaolin, aluminum silicates, and starch. A large number of powders are used as surgical dressings. Their virtues are due to their mechanical properties, and not to their bactericidal action.

Preparations

Adeps (U. S. P., B. P.), lard; the prepared internal fat of the abdomen of the pig, purified by washing in water, melting and straining.

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ADEPS BENZOINATUS (U. S. P., B. P.), benzoinated lard, is prepared from lard by the addition of benzoin, which is believed to preserve it from becoming rancid, and certainly conceals the odor.

UNGUENTUM ALBUM (U. S. P.), white ointment, consists of wool fat, white wax and white petrolatum. It is the base of many ointments.

ADEPS LANÆ HYDROSUS (U. S. P., B. P.), hydrous wool-fat, lanolin, the purified fat of sheep-wool, mixed with not more than 30 per cent of water.

ADEPS LANÆ (U. S. P., B. P.), wool-fat without water.

ALCOHOLIA LANÆ (B. P.), wool alcohols.

UNGUENTUM ALCOHOLIUM LANÆ (B. P.), ointment of wool alcohols.

UNGUENTUM SIMPLEX (B. P.), containing wool-fat and paraffins.

Wool-fat consists of cholestrin esters with some impurities, does not become rancid, and differs from the older fats in being miscible in twice its weight of water without losing its ointment consistency. Lanolin is very often used as an emollient application, as well as to form a basis for more active drugs. The unhydrated wool-fat is too sticky to be satisfactory. The hydrated form is generally too hard to be used as an ointment and is therefore diluted with soft paraffin (3 parts) or olive oil (equal parts).

PETROLATES OR PARAFFINS. When the more volatile constituents of petroleum are distilled off, there remains a number of higher hydrocarbons, chiefly of the marsh gas series, which are used in medicine as emollients. The lower of these hydrocarbons are fluid at ordinary temperatures and are known as:

PETROLATUM LIQUIDUM (U. S. P.), PARAFFINUM LIQUIDUM (B. P.), a colorless, oily transparent liquid without odor or taste. When these are removed there remains:

PETROLATUM (U. S. P.), and PETROLATUM ALBUM (U. S. P.), PARAFFINUM MOLLE (B. P.), soft petrolate, which has the consistency of an ointment, is yellow or white in color, and is liquefied a few degrees above the temperature of the blood. When the distillation is carried further, the residue is solid at ordinary temperatures, and is known as

PARAFFINUM DURUM (B. P.), or hard paraffin, which melts at a somewhat higher temperature than petroleum jelly.

Soft petrolatum is more extensively used than the others as an emollient and as a basis for ointments, and has the advantage over lard that it does not become rancid; as a general rule it is too soft but may be made of the proper consistency by the addition of wool-fat or of starch or zinc oxide (equal parts); or the UNGUENTUM PARAFFINI (B. P.), containing hard and soft paraffin and beeswax, may be employed.

Several OILS are also used as emollients.

OLEUM OLIVÆ (U. S. P., B. P.), olive oil, a fixed oil obtained from the ripe fruit of the olive, Olea europea.

OLEUM AMYGDALÆ EXPRESSUM (U. S. P.), OLEUM AMYGDALÆ (B. P.), a fixed oil expressed from bitter or sweet almonds. It is to be distinguished from the volatile oil obtained from the bitter almonds. The fixed oil contains no prussic acid.

UNGUENTUM AQUÆ ROSÆ (U. S. P.), cold cream, is formed of white wax, spermaceti, oil of almonds, and some borax, scented with rose water.

UNGUENTUM AQUOSUM (B. P.) contains beeswax, soft paraffin, olive, cotton-seed or sesame oil and water, with some borax.

UNGUENTUM HAMAMELIDIS (B. P.), ointment of hamamelis.

OLEUM GOSSYPII SEMINIS (U. S. P., B. P.), cotton-seed oil.

OLEUM SESAMI (B. P.), sesame oil.

These all resemble each other in their composition, and may be used as emollients. Olive oil is applied externally as an emollient and sedative to inflamed surfaces and is used extensively in the preparation of liniments, plasters, etc. Almond oil is usually preferred for cold creams and toilet preparations.

Wax (CERA), spermaceti (CETACEUM) and suet (SEVUM) are of harder consistency than lard, and are added to the other emollients to make them firmer, which is especially desirable in hot climates and in summer.

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GLYCERINUM (U. S. P., B. P.), glycerin, a liquid obtained by the decomposition of animal or vegetable fats or fixed oils, and containing not less than 95 per cent of absolute glycerin, $C_3H_5(OH)_3$; clear, colorless, of a syrupy consistence, oily to the touch, with a sweet taste and no odor, soluble in water and alcohol.

Glycerin is used as a solvent for a number of other drugs, the preparations being known as GLYCERITES (U. S. P.), GLYCERINES (B. P.).

Glycerin is somewhat irritant to the unbroken skin, when it is applied in the pure form, and even diluted glycerin causes pain and smarting when it is applied to unprotected surfaces such as cuts or burns, but the pain soon disappears, and glycerin then acts as a protective. The irritation is due to the glycerin abstracting the fluids of the tissues owing to its avidity for water. Diluted with one or two volumes of water or rose water, glycerin is useful as an emollient in conditions of irritation of the skin and the lips from exposure to cold, and in similar conditions. Glycerin is not a disinfectant except in strong solution, in which it probably acts by the withdrawal of water from the microbes.

OLEUM THEOBROMATIS (U. S. P., B. P.), cacao-butter, a fixed oil expressed from the seeds of Theobroma cacao, forms a yellowish-white solid having a faint, agreeable odor and a bland chocolate taste. It melts a little below the temperature of the body. Cacao-butter is used almost exclusively to form suppositories, in which astringents and other remedies are incorporated. When introduced into the rectum, they melt and the active principle is liberated.

SAPO DURUS (U. S. P., B. P.), hard soap, white Castile soap, is prepared from soda and olive oil.

SAPO MOLLIS MEDICINALIS (U. S. P.), SAPO MOLLIS (B. P.), soft soap, sapo viridis, a soap made from potash and olive oil.

SAPO ANIMALIS (B. P.), curd soap, soap made with sodium hydroxide and purified animal fats consisting chiefly of stearin; it contains about 30 per cent of water.

These soaps are used in therapeutics as ingredients of liniments and plasters. Water containing soap is often thrown into the rectum as an enema, and in infants a soapstick inserted into the anus generally provokes evacuation of the bowels in a few minutes.

Soaps impregnated with antiseptics, such as perchloride of mercury, carbolic acid, tar, or iodine, are often used to disinfect the hands.

The chief preparations in which soap is used in the pharmacopeias are:

LINIMENTUM SAPONIS (B. P.), soap liniment, and

LINIMENTUM CAMPHORÆ ET SAPONIS (U. S. P.), both contain about 4 per cent of camphor and are used as mild counter-irritants.

LINIMENTUM SAPONIS MOLLIS (U. S. P.).

The liniments consist of alcohol with soap in suspension, perfumed with volatile oils, and are mildly irritant to the skin. They are used largely as bases for other liniments.

PLASTERS are sticky, adhesive substances which are chiefly used to give mechanical support, but which are often impregnated with active remedies in order to elicit their local action on the skin. The basis of many of the plasters is lead plaster, which is obtained by the action of lead oxide on olive oil and consists for the most part of lead oleate.

EMPLASTRUM COLOPHONII (B. P.), adhesive plaster.

Court plaster is formed from isinglass, the dried swimming bladder of several species of sturgeon, which is dissolved in water, alcohol, and glycerin, and painted on taffeta. Isinglass differs from lead plaster and its derivatives in being transparent, so that if it is spread on a flesh-colored cloth, it disfigures the hands and face less than the others.

Lead plaster, adhesive plaster and isinglass plaster are used only to cover and protect cuts and abrasions, and to keep the edges of wounds in apposition. The adhesive plaster and isinglass plaster are superior to lead plaster, as they stick more firmly. It is perhaps unnecessary to add that plasters are always applied spread on cloth.

Another series resembling the plasters in their sphere of usefulness is formed by the COLLODIA. Their basis is pyroxylin, or soluble gun-cotton, which is formed

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from cotton by the action of sulfuric and nitric acids, and which consists of a mixture of nitrates of cellulose. Collodion is formed by dissolving pyroxylin in a mixture of alcohol and ether. When these evaporate, there remains a fine layer of pyroxylin, which protects the surface to which it is applied and gums the edges of slight cuts together. This collodion is rendered less brittle by the addition of Canada turpentine and castor oil in small proportions, and is then known as flexible collodion.

CATAPLASMA KAOLINI (B. P.), a poultice of kaolin with the addition of boric acid, methyl salicylate, oil of peppermint, thymol and glycerin.

COLLODIUM (U. S. P.), collodion.

COLLODIUM FLEXILE (U. S. P., B. P.), flexible collodion.

KAOLINUM (B. P.), kaolin, a native aluminium silicate.

PYROXYLINUM (U. S. P., B. P.), soluble gun-cotton, colloxylin.

TALCUM PURIFICATUM (U. S. P.), talc, a purified, hydrous magnesium silicate.

TERRA SILICEA PURIFICATA (U. S. P.), siliceous earth or kieselguhr, a purified form of silica.

II. SKIN IRRITANTS AND COUNTER-IRRITATION

The practice of applying irritants to the skin in internal diseases is one of great antiquity. The theories on which this therapeutic method is based have changed with the advance of medical knowledge, until, no explanation satisfactory to modern skepticism being forthcoming, the use of these remedies has fallen into a certain disrepute in recent years. The old theory of revulsion or derivation was at first based on the belief that disease was a malignant entity or humor, which might be drawn from the deeper organs to the surface by means of irritation of the skin. Later, it was supposed that the congestion of the diseased organs might be relieved by the withdrawal of fluid to the skin, and this belief has been held in more or less modified forms in quite modern times. In addition, it was recognized very early that irritation of the skin relieved pain in many instances. The means by which the skin irritation was attained were extremely numerous and varied; large numbers of drugs have been used, and in addition mechanical devices of all kinds were employed, such as burning, electrical currents, or the introduction of setons. In many of these the idea of irritation was combined with that of leaving a way of escape for humors. This latter is only of historical interest, but the practice of relieving internal organs by external irritation or *counter-irritation* persists still, and perhaps merits more attention than it receives at the hands of many physicians.

The effects of an irritant applied to the skin are local and remote. The first symptoms of irritation are congestion and redness of the part, and many drugs which produce only this degree of irritation in ordinary circumstances, are known as *Rubefacients*. Stronger irritants cause blistering, and are called *Vesicants*, while some drugs which cause irritation and small discrete suppurations, receive the name of *Pustulants*.

Local Symptoms.—The application of an irritant to the skin causes a feeling of warmth, and often of itching, which may later become intensified into actual pain. The skin becomes red, congested, warm, and at first is more sensitive to touch and painful stimuli, though

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the sensitiveness is afterward lessened. This condition persists for a longer or shorter time according to the nature of the irritant, and then passes off slowly. Very often desquamation follows, if the rubefacient has acted for some length of time. Stronger irritation is followed at first by the same results, but soon small globules of fluid appear below the epidermis, and these coalesce so as to form a large accumulation of fluid, which raises the epidermis completely off the true skin, forming a blister. If the irritant be removed, the fluid of the blister undergoes a slow absorption, so that in the course of a few days the epidermis forms an empty sack, which, however, is not obliterated by the adhesion of the walls. If the blister be opened, the sensitive dermis is exposed, and the secretion of fluid continues for some time, until a new epidermis has been formed.

The distinct and separate points of inflammation caused by the pustulants are due to their affecting the orifices of the skin glands and not the intervening tissue. They cause the same sense of warmth and prickling of the skin as other irritants, but even in the earlier stages of their action small, dark-red, raised points are observed, exactly as in some of the exanthemata, and these afterwards form small abscesses. If the application be persisted in, these discrete abscesses may burst through the intervening tissues and become confluent, and large abscesses have thus been formed in the skin. When the irritant is removed before the formation of pus, the inflammation of the skin slowly subsides and the epidermis peels off as after the milder irritants. Pustulants are seldom employed at the present time; croton oil applied vigorously may induce pustulation, and tartar emetic was formerly largely used for this purpose.

The local effects of the rubefacients and vesicants are identical with those of acute inflammation. The pain and discomfort are due to the action on the nerve terminations, while the redness and swelling betray the local dilatation of the vessels. This latter appears to be due to a reflex from the sensory terminations to the vasodilator nerve ends on the vessels; the central nervous system is not involved in this reflex, for it occurs after division of the nerves of the part, but not after the peripheral fibers have degenerated; it is thus of the nature of an axon reflex (Bruce). The dilatation of the vessels and the slowing of the blood current in them lead to the transudation of fluid and leucocytes into the tissues, especially at the points where the irritation is greatest, and the accumulation eventually pushes off the horny epidermal layer from the living layers and forms a blister. The fluid in the blister has been shown to contain some of the irritant, which diffuses into it through the epidermis. The edema and swelling are not confined to the skin, but extends into the subcutaneous tissue and the more superficial layers of muscle.

If the irritation be continued long enough, suppuration may commence in the blister and lead to deep erosion of the tissues.

Remote Action.—Local irritation cannot exist without causing certain general changes which affect the whole organism, and which arise from reflex stimulation. Much light has been thrown on the subject by

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the observations of Mackenzie and Head, who found that visceral disease is often accompanied by tenderness of the skin and underlying muscles, and that the pain arising in these cases is referred to this area of skin and not to the organ involved. Thus in painful diseases of the stomach, tenderness is often found in the skin and muscles of the epigastrium, while in esophageal stricture, pain may be referred to a point near the angle of the scapula and to another in the neighborhood of the apex beat. Similarly in heart disease, pain is often felt in the left chest-wall and shoulder extending down the left arm. These points are, of course, only connected with the diseased organ by means of nerve-fibers, and it thus appears that impulses from such an organ arouse a condition of heightened sensibility in the region of the cord on which they impinge; this

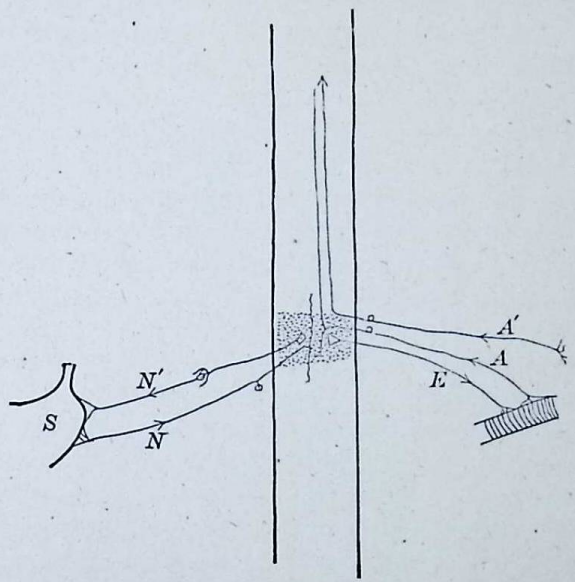

FIG. 8.—Diagram to illustrate the effects of visceral disease on sensation (after Mackenzie). *S*, diseased viscus, with afferent nerve fiber *N* and efferent fiber *N'* issuing from the same area of the spinal cord. The impulses from the diseased area induce a condition of heightened sensibility in the shaded area. *E*, a motor nerve fiber to muscle, which carries more impulses than usual from the area in the cord and thus leads to a tonic contraction of the muscle. *A*, the afferent nerve from the muscle and A' from the skin entering the cord in the sensitive area and thus giving rise to the sense of pain and tenderness, which is referred to the peripheral distribution in the skin and muscle.

affects all the synapses in the neighborhood (Fig. 8), so that impulses from very different structures may be altered by the affection of one. The sensation of pain aroused by this exaggerated sensibility is of course referred to the periphery, not to the focus in the cord, and this gives the impression of tenderness in the skin and muscles. It therefore seems probable enough that an affection of these superficial areas may affect the corresponding internal organ more than the rest of the body, and this is exactly what is required to explain the benefits derived from the use of counter-irritants. It is especially noticeable that several of the skin areas affected by internal disease are precisely those points at which experience has shown irritation to be most beneficial (Fig. 9). Thus the application of a blister over the epigastrium has long been recognized

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as a means of relieving gastric disorders. Similarly the old treatment of iritis by means of a blister on the temple may be justified by the fact that Head found areas of tenderness on the temple accompanying this disease.

The exact nature of the effects of counter-irritation on the internal organs has not been ascertained, but it would seem most probable that an alteration in the caliber of the vessels is induced. These alterations may be accompanied by changes in the activity of the organs; for example, there seems good reason to believe that in many cases irritants applied to the abdomen produce evacuation of the bowels. The most obvious effect of counter-irritation very often is

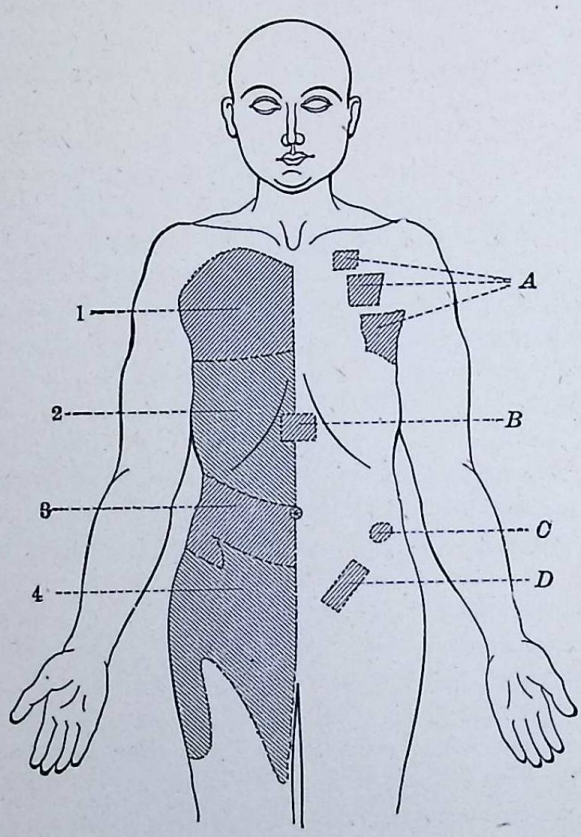

FIG. 9.—The right side is divided into segments which correspond to some of the skin areas in which Head found tenderness in internal diseases. 1. Area of tenderness in disease of the lungs. 2. In diseases of the stomach. 3. In ovarian disease. 4. In disease of the Fallopian tubes and other appendages. On the left side are represented the points of application of counter-irritants in disease of the lungs (*A*), of the stomach (*B*), of the ovary (*C*), and the uterine appendages (*D*).

the relief of pain, and this seems explicable in the light of the observations of Mackenzie and Head. For if the pain in visceral disease is due to the disorder of the synapses in the spinal cord at the level at which the fibers from the viscus and from the superficial tissues meet, it is possible that new impulses reaching this area from the skin may alter its condition or may occupy a common path to the brain to the exclusion of impulses arising from the seat of disease. Or, if the pain arises from cramp in a superficial muscle innervated from the same level of the cord as the diseased viscus, an irritant applied over the muscle may increase its circulation and warmth and thus relieve the cramp and the pain.

Besides these physiological effects of counter-irritation, it must not be forgotten that a great impression is produced on the patients, and that some of the benefit may be due to suggestion.

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Therapeutic Uses.—Local irritants are applied occasionally to produce an alteration in the nutrition and blood supply of the skin itself and of the subcutaneous tissues. Thus in some chronic inflammatory conditions, with effusions into, or indurations of the subcutaneous tissues, the improvement of the circulation produced by slight irritation may be of benefit. An example of this is the treatment of ulcers of old standing with irritants. Another case in which a slight inflammatory attack causes very obvious improvement is in corneal opacity, which may be removed entirely in some cases by the acute inflammatory reaction produced by such irritants as abrine. Probably a similar effect is produced on subcutaneous effusions, as in bruises. It has been found experimentally that when abscesses in the subcutaneous tissues are treated with mild irritation of the skin over them, they improve more rapidly than controls left without treatment; the increased blood supply leads to a larger supply of leucocytes and protective substances around the inflammation than would otherwise be present. Similarly, the absorption of pigments injected into the rabbit's ear is much accelerated by the application of irritants to the skin over the part. Sollmann induced a series of nodules in the skin of his forearm by intracutaneous injections and found that their disappearance was hastened by the application of iodine over them. For these purposes only the milder irritants are required, in fact vesication may do more harm than good.

Mild irritation alters the sensitiveness of the sensory organs of the skin, and heat is often applied to alleviate pain and discomfort in the skin itself. In other instances pain is increased by heat, and, in fact, it is sometimes applied in the treatment of local anesthesia, with the object of rendering the surface more sensitive. In many forms of skin disease, mild irritants are found to be of benefit; this is sometimes attributed to their antiseptic action, but the slight irritation is undoubtedly of greater importance.

Counter-irritants were formerly used in a large number of diseases, but their use has declined and they are now employed only rarely. As a general rule they are placed over the affected organ, and this corresponds fairly in most cases of disease of the trunk with Head's area of skin tenderness. In the head, however, the segmental arrangement has been rendered very irregular by the compression in development, and counter-irritants are often found to be most effective when placed at some distance from the seat of pain, *e. g.*, behind the ear in some forms of facial neuralgia and neuritis. Their action is very uncertain, but their application is often followed by great relief, more especially of pain.

An enormous number of drugs produce irritation of the skin, and it would be idle to attempt to enumerate them here. In many instances, however, the irritant action is insignificant in comparison with the other effects produced, and these will, therefore, be discussed elsewhere; among these are found some of the alkaloids, the acids and alkalies, and many other inorganic preparations. Irritation of the skin may also be produced by heat and cold, and in fact burning in various forms was formerly used as a means of counter-irritation. Heat

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is still employed to cause irritation of the skin and subcutaneous tissues, and to promote their circulation. Thus, poultices and hot water compresses are beneficial in many local inflammations, though the same effects may generally be obtained by the use of the milder irritants. Somewhat similar results may be obtained in the trunk by dry cupping, in which the blood is drawn to the diseased superficial tissue by applying a glass tightly to the skin and exhausting the air in its interior, but this procedure is rarely used now. Cold is also used as a means of inducing local anesthesia. The application of a spray of ethyl chloride by its cooling effect or packing an extremity in ice induces sufficient anesthesia to permit surgery on the part thus treated.

Apart from those drugs in which the irritation of the skin is merely an incident in a wider general action, there are a number of preparations which are used almost exclusively for this purpose. They may be divided into three classes: the volatile irritants, such as turpentine oil; the mustard series, some of which are also volatile; and those which are either non-volatile or only boil at high temperatures, such as cantharidin.

1. The Turpentine Oil Group

Under the volatile irritants may be included a large number of the ethereal oils and many members of the methane and of the aromatic series; but among the ethereal oils those which possess a low boiling point, that is, those which contain a large proportion of terpene, with comparatively little oxygen, are found to possess a more penetrating action than the others. At the same time, the taste and odor of these oils is often less pleasant than that of the others, so that they are less used as flavors and carminatives. The oils derived from the *Coniferæ* have, for this reason, been more largely used than the others for their effect on the skin, although several other volatile preparations are recognized by the pharmacopeia for this purpose. The action of these oils is similar in other respects to that of the general group (see p. 207), so that it need not be discussed here.

Therapeutic Uses.—Turpentine oil is used externally as a rubefacient, and differs from mustard and cantharidin in its greater penetrating power. It is not so irritant; however, it blisters after long application, and the vesication produced is very painful and heals slowly, from the vapor penetrating into the deeper tissues. It is, therefore, employed to produce rubefaction only, and ought to be removed when this is attained. For this purpose any of the liniments of the group may be employed, or a more intense action may be got from the "turpentine stupe," which is made by dipping flannel in hot water, wringing it dry, and then dropping warm turpentine oil on it. Turpentine preparations are used especially in rheumatic affections of the joints or muscles, and in sciatica. Turpentine oil is a fairly strong antiseptic, and is less irritant than many of the more powerful ones.

Some remedies which produce irritation of the skin of approximately the same degree as turpentine oil, but which are discussed elsewhere are camphor, chloroform, dilute acetic acid, ammonia, alkalies, alcohol, iodine and some of the heavy metal preparations.

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PREPARATIONS

OLEUM TEREBINTHINÆ RECTIFICATUM (U. S. P.), OLEUM TEREBINTHINÆ (B. P.), is formed from ordinary oil of turpentine by redistillation and consists of a mixture of terpenes ($C_{10}H_{16}$).

EMULSUM OLEI TEREBINTHINÆ (U. S. P.). Dose, 2 cc.

LINIMENTUM TEREBINTHINÆ (B. P.).

LINIMENTUM TEREBINTHINÆ ACETICUM (B. P.) is formed by mixing turpentine, glacial acetic acid, and camphor liniment.

2. Mustard

Black Mustard, the seeds of *Brassica sinapioides*, contains a glucoside, *Potassium Myronate* or *Sinigrin*, and a ferment, *Myrosin*, which decomposes it in the presence of water into dextrose, potassium bisulphate and allyl-isosulphocyanate, or volatile oil of mustard.

$$\underset{\text{Sinigrin}}{C_{10}H_{18}KNS_2O_{10}} = \underset{\text{Volatile oil}}{C_3H_5NCS} + \underset{\text{Dextrose}}{C_6H_{12}O_6} + KHSO_4$$

Action.—Volatile oil of mustard is intensely irritant when applied to the skin, and if left long enough produces blistering which is more painful than that caused by cantharides, and is said to heal less readily. This is probably due to the oil penetrating more deeply into the tissues, and thus setting up more extensive inflammation. Mustard is accordingly used only to induce rubefaction, and ought to be removed before actual vesication occurs. When the crude drug is moistened and applied to the skin, the oil is formed only slowly, so that the longer it remains applied, the more intense is the action. The glucoside in itself has little or no action, and the products of its decomposition are harmless, with the exception of the oil.

Uses.—Mustard is largely used as a condiment and to promote appetite, but is never prescribed for this purpose. In large quantities it causes violent irritation of the stomach and bowel, with vomiting, purging, acute pain and tenderness in the abdomen, and collapse. Mustard and warm water is a convenient emetic in emergencies, as in cases of poisoning.

The plaster or leaf (charta) is the form in which it is generally used in therapeutics. It contains the glucoside, which is slowly decomposed by the ferment when the plaster is dipped in warm water for a few minutes before application. Another popular application is the mustard poultice, in which powdered mustard is sprinkled on an ordinary poultice. Mustard is also added to baths occasionally when slight irritation and consequent congestion is desired over a large surface. For this purpose 2 to 4 teaspoonfuls of the dry powder are added for each gallon of water. In preparations of mustard it is important to avoid a temperature of over 60° (140° F.), as the ferment is destroyed above this. The plaster is left on the skin only for fifteen to thirty minutes when it is used as a rubefacient.

PREPARATIONS

SINAPIS NIGRA (U. S. P.), the dried ripe seeds of Brassica nigra.

EMPLASTRUM SINAPIS (U. S. P.), black mustard powder rendered adhesive by India-rubber, applied to sheets of paper and dried.

ALLYLIS ISOTHIOCYANAS (U. S. P.), derived from black mustard.

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3. Cantharidin

Another series of local irritants comprises non-volatile substances, of which cantharidin ($C_{10}H_{12}O_4$) is the best known. It is an anhydride and when acted on by bases form cantharidates, which resemble it in action. It is found in Spanish fly (*Cantharis vesicatoria*, or *Lytta vesicatoria*) and in several allied species of *Coleoptera* (beetles).

Action.—Applied to the *skin*, cantharidin produces redness, smarting and pain, followed very soon by small vesicles, which later coalesce into one large blister. This is much less painful than the vesication produced by mustard, because less of the irritant penetrates into the deeper tissues than in the case of the volatile mustard oil. If the blister be broken, however, and the unprotected dermis be allowed to come in contact with the irritant, violent inflammation with much pain, suppuration and even sloughing may follow.

When large quantities of cantharidin are given *internally*, the same irritant action takes place along the alimentary tract. If taken in solution, blisters arise in the mouth and throat, and the pain and swelling in the esophagus may be so acute as to prevent swallowing. The irritation of the stomach produces vomiting, followed by purging with excruciating pain in the abdomen, and all the symptoms of shock and collapse.

Cantharidin is absorbed from the alimentary canal, and also to a lesser extent from the skin, but has no important action on the internal organs, with the exception of those by which it is eliminated. Vomiting occurs on subcutaneous injection from some of the poison being excreted into the alimentary tract. Comparatively small quantities irritate the bladder, and cause a constant desire to micturate, with pain in doing so. In somewhat larger amount it sets up an acute nephritis with albuminuria, pain in the kidney region, and sometimes blood in the urine. The inflammation of the bladder and urethra produces intense pain and often priapism; in women abortion is said to occur occasionally, and in both sexes the irritation may lead to increased sexual desire.

Therapeutic Uses.—This drug is at present rarely used and exclusively as a skin irritant, and more particularly as a vesicant. The plaster is the form generally used. It is to be noted that in order to produce actual blistering, the plaster has to remain in contact with the skin some eight to ten hours, but an equal effect may be achieved by replacing the plaster by a hot poultice after four to six hours, when the skin irritation has reached the stage of redness. The ointment is said to induce blistering sooner than the plaster. Cantharis is also used to cause rubefaction and commencing vesication (flying blister); this may be done by the use of the plaster.

Cantharidin is liable to be absorbed from the skin, and its application is therefore avoided where there is any tendency to renal inflammation.

Cantharis has been used as an aphrodisiac, and several cases of poisoning have occurred from its administration for this purpose.

In cases of **Poisoning** with cantharides, the stomach ought to be emptied as rapidly as possible by the stomach tube, provided the esophagus allows of its passage. Demulcents and albuminous substances are of use in slowing the absorption, but all oily or fatty bodies must be avoided, as they tend to dissolve the cantharidin and thus promote its absorption. Opium may be given for the pain, and if collapse sets in, the ordinary measures must be taken to combat it. Ellinger states that the action on the kidney in rabbits is more severe

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when the urine is acid than when it is alkaline, and this suggests the treatment of the renal symptoms with alkalies.

PREPARATIONS

B. P.

CANTHARIDINUM ($C_{10}H_{12}O_4$), obtained from various species of Cantharis or of Mylabris.

EMPLASTRUM CANTHARIDINI, containing 0.2 per cent.

LIQUOR EPISPASTICUS, blistering liquid, 0.4 per cent.

Toxic Skin Irritants

Poison Ivy and Poison Oak.—The commonest form of poisoning in the United States is the skin eruption produced by the leaves of poison ivy and poison oak (*Rhus toxicodendron* and *venenata*), which Pfaff showed to be due to the presence of a neutral body, Toxicodendrol. The effects of poison ivy can arise only from touching the plant, the poisonous principle not being volatile. Very minute quantities of toxicodendrol are sufficient to produce skin eruptions, however, 0.001 mg. causing distinct symptoms in susceptible persons. The popular belief that skin affections can be induced by approaching the plant, without actually touching it, is probably accounted for by the fact that the eruption may not appear until several days after contact, and that poison ivy is very frequently mistaken for harmless climbing plants. The statement that the poison ivy does not affect some individuals is also probably erroneous, though persons of delicate skin are undoubtedly more susceptible. Immunity is not acquired for the poison by repeated attacks of dermatitis. Other species of *Rhus*, *e. g.*, *R. vernicifera* (the lacquer tree) also give rise to dermatitis.

In the dermatitis from poison ivy, the skin is washed and scrubbed with soap and water, or with alcohol. Ointments and oily liniments are to be avoided, as they dissolve the toxicodendrol and tend to spread it over the skin and thus produce further inflammation. For the same reason, the alcohol used to wash the part must be removed entirely, as the poisonous principle is soluble in it, while insoluble in water. Potassium permanganate solution is an efficacious application particularly if an aqueous solution of sodium bicarbonate is first applied and allowed to dry. A 1 per cent solution of potassium permanganate is then applied to the affected area.

Eruptions similar to that from poison ivy arise from contact with a number of other plants of which the best known is the *Primula obconica;* this plant secretes some unknown substance which is intensely irritant to the skin of many people, and has frequently given rise to severe inflammation in gardeners and others. Cash found an alkaloid obtained from East India Satinwood (*Chloroxylon*) equally irritant when applied to the skin; the dermatitis from these bodies often appears only two to three weeks after contact with them, and even after application of the poison. Dermatitis from other woods has been described *e. g.*, S. African boxwood, W. African mahogany and teak.

A number of the Ranunculaceæ are irritant to the skin like cantharides, but the active constituent has not been definitely determined. *Mezereum*, which

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was formerly official, is similarly irritant, apparently from the presence of an irritant oil. *Cardol*, found in the fruits of Anacardium occidentale and in Semecarpus anacardium, is a very powerful irritant, and has been used to a limited extent as a vesicant. Cardol is probably a mixture of a number of substances, but it is unknown to which of these it owes its activity. *Euphorbin* is said by Buchheim to be the irritant principle in the Euphorbia resin (*Euphorbia resinifera*, etc.), and to resemble cantharidin in its anhydride form, but the salts and the euphorbic acid which is formed from them by acids are inactive. A very poisonous member of the *Euphorbiaceæ* is the Manicheel tree, growing in the West Indies, and it apparently belongs to this series.

Dichlorethylsulphide, or Thiodiglycolchloride $(CH_2ClCH_2)_2S$, the notorious "Mustard Gas" of the First World War, is a synthetic substance which has an irritant and destructive action on the skin, and proves fatal through pulmonary irritation when inhaled in even minute quantities. It is a volatile oily fluid. Effects of contact with the fluid or vapor come on after a latent period of some hours. These consist of inflammation, leading sometimes to vesication or necrosis. Mucous membranes, *e. g.*, of the eye and of the alimentary and respiratory tracts are affected earlier than the skin. In addition to mustard gas, modern warfare has contributed a number of other irritant agents. The **Lacrimators** are substances which induce irritation to the eyes and include relatively non-toxic irritants as well as highly fatal poisons. The former have been used to disperse mobs and force persons from hiding. Among the simple lacrimators are chloracetophenone, brombenzyl cyanide, ethyliodoacetate, benzyl iodide and bromide and brommethylethylketone. Toxic lacrimators include bromacetone, chlorpicrin, chloracetone, iodoacetone and phenylcarbylamine.

A number of arsine derivatives were also introduced in chemical warfare. These comprise the **Sternutators** which are solids and are dispersed as a dust. This group includes diphenylcyanarsine, diphenylchlorarsine, ethyldichlorarsine, etc.

Other lung irritants used as war gases are chlorine gas, phosgene and dimethylsulfate which are used in industry and are occasionally the cause of poisoning.

Nitrogen Mustards.—In this connection mention may be made of the nitrogen mustards which resemble mustard gas and its derivatives in chemical formulæ, except for the substitution of a nitrogen atom for the sulfur present in the latter. The nitrogen mustards act on malignant tissues and for this reason have been used experimentally in the treatment of such disorders as Hodgkin's disease, multiple myeloma and the lymphomata. Their value in these disorders remains to be established but the preliminary results have opened a new field of investigation in the treatment of these neoplasia (Rhoads).

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III. VOLATILE OIL SERIES

The group of volatile, ethereal, or essential oils contains a large number of preparations in the pharmacopeias of all countries. These oils are obtained from plants by distillation, or more rarely by pressure, and must be distinguished by the student from the fatty or fixed oils, which are non-volatile. The volatile or ethereal oils are found chiefly in the fruits and flowering parts of plants, and are very widely diffused through the vegetable kingdom, though some orders, such as the Labiatæ, Umbelliferæ, Aurantiaceæ, Cruciferæ, and Coniferæ, are pre-eminent in their production. They are all strongly odorous, and are therefore used in perfumery, and to conceal nauseous odors and tastes in medicine.

Their composition is extremely variable. The commonest constituents are *Terpenes*, and some oils contain these only, while in a few oils no terpene has been found (Attar of Roses). Terpenes are hydrocarbons of the aromatic series, and possess the general formula $(C_5H_8)_n$. The great majority of them, or the terpenes proper $(C_{10}H_{16})$, are combinations of a dihydrobenzene with propyl and methyl $(C_6H_4(H_2)C_3H_7CH_3)$. Some twelve terpenes of this formula are known, varying in their chemical structure and in their stereometrical form. Another group of these hydrocarbons is formed by the *Sesquiterpenes* $(C_{15}H_{24})$, while a few *Diterpenes* $(C_{20}H_{32})$ are known. Some volatile oils consist of these hydrocarbons only, but most of them contain in addition some oxidized aromatic substances, such as phenols, ketones, aldehydes, acids, and their compounds; as instances of these may be cited camphor, thujon (from oil of absinthe), sabinol (oil of savine), safrol, thymol, eucalyptol, myristicin and vanillin. Many of these oxidized products crystallize out when the volatile oil is cooled sufficiently, and especially on long standing, and the resulting solid is known as a *Stearoptene*, while the fluid remaining is sometimes called *Elæoptene*. The oils containing oxygen are not so volatile as the pure hydrocarbons, but the odor is often due chiefly to the oxidized substances. A very few oils contain nitrogenous bodies, generally in the form of cyanides, while, on the other hand, the majority of the volatile oils of the Cruciferæ contain sulfur bodies, which lend them a pungent disagreeable odor, quite different from that of the other oils.

The volatile oils are generally clear, colorless fluids, although some of them are green or blue in color. After long keeping they often acquire a yellowish color and an acid reaction, from the formation of resins. They are generally light, sparkling fluids, but the oils of copaiba and cubebs are more viscid. They are insoluble in water except in very small amount, which, however, is enough to lend their characteristic odor to the solution; in strong alcohol, ether, benzene, chloroform, and fixed oils, they are freely soluble.

Many of the plants from which the volatile oils are obtained possess other active constituents, such as bitters, and as many of the preparations used in therapeutics are formed, not from the distilled oils, but from the crude parts of plants, it must be noted that the oil is not the only active principle in them.

Action Externally.—The volatile oils all possess antiseptic properties, which are doubtless due in part to their volatility and their solubility in lipoids enabling them to penetrate readily into protoplasm. Many of them appear to be more germicidal than carbolic acid in favorable

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circumstances, but they are generally too insoluble in water to be employed easily in surgery.

Applied to the skin, they cause redness, itching and warmth, owing to a local dilatation of the vessels, which may be due to the penetration of the oil to the cutaneous arterioles or veins, or to a local reflex from the irritated terminations of the sensory nerves. When painted on the mucous membranes, such as those of the eye or nose, or on wounds, the volatile oils cause similar irritation, which is betrayed by redness and congestion, pain and smarting.

Action on the Alimentary Canal.—Strong solutions of the oils have generally a hot, burning taste, and if kept in the mouth, cause redness and irritation of the mucous membranes, although some of them induce a sense of coolness at first. At the same time the organs of smell are affected by these oils, which are almost all possessed of characteristic odors. The irritation of the mouth leads to a reflex secretion of saliva, which is often very profuse. The antiseptic action of the oils is exercised in the mouth as elsewhere, and may have a beneficial effect in some conditions.

On passing into the stomach, the oils cause the same sensation of warmth in the gullet, and this is accompanied by a sense of well-being and comfort, the appetite is often increased, and any feeling of distention after meals is relieved. This is often attended by the eructation of quantities of gas. Substances which produce these effects in the stomach are known as *carminatives*, and many explanations of their action have been offered. The antiseptic action may occasionally play a part in the carminative action, and possibly the secretion may be encouraged by the slight irritation and by the agreeable odor and taste; the activity of the ferments is retarded rather than augmented. The movements and tone of the stomach are decreased by small quantities of the oils applied to the mucous membrane; this weakening action probably extends to the sphincters, and their relaxation may explain the relief of the feeling of distention and the eructation of gas from the stomach after the administration of these oils. In the intestine small quantities generally increase the movements, while larger ones decrease them; sometimes the bowel is relaxed owing to a reflex arising from the action on the stomach. In practice they often relieve intestinal flatulence and distention and lessen the spasms which cause colic. Small quantities are incorporated in the preparations of the more powerful purgatives to lessen the pain and griping which these are liable to induce.

An indirect effect of the local action on the gullet and stomach is slight flushing of the skin from dilation of its vessels, along with a feeling of warmth and relief of chill. This appears to arise from a reflex traveling from the sensory ends in the mucous membranes to the vasomotor center in the medulla oblongata and is most frequently seen under camphor.

Excretion.—Many of the terpenes are oxidized to phenols in the body and are then excreted in the urine, for the most part in combination with glycuronic or sulfuric acid. Traces pass out in the expired air and impart an odor to the breath. The urine also contains some in

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a free form and may thus smell of the original oil or of some of its derivatives. Some of the constituents of the oils are oxidized to acids and excreted in the urine as salts.

In the course of excretion, some of the oils cause irritation of the lungs and kidneys, so that some of them are employed to increase the bronchial secretion, while others have a distinct diuretic action.

Poisoning.—The various oils differ a good deal in their activity while resembling each other closely in the general characters of their effects. All of them may produce marked irritation of the stomach and bowel when given in large quantities, but the oils of pansy, sage, and English pennyroyal are distinguished especially by the violent inflammation they cause, and by the frequency with which fatal poisoning occurs from their use. The symptoms are those of acute gastric, intestinal, and often renal irritation: vomiting, purging, acute pain in the abdomen, blood in the stools and in the vomited matter, collapse, weakness of the pulse and respiration, anuria, or albumin and blood in the urine, and convulsive attacks ending in coma and death. Great hyperemia of the abdominal organs, often blood in the peritoneal cavity, and sometimes acute inflammation of the kidney are the chief postmortem appearances. Though they do not increase the uterine movements directly, the congestion of the organs of the abdomen may cause abortion in pregnancy, or increase the menses, and in most cases of poisoning, these oils have been taken to induce abortion; too often they have proved fatal without this end being achieved. Oil of eucalyptus has frequently given rise to poisonous symptoms.

Action on Nervous System.—In large quantities, some of the volatile oils (the oils of wormwood, nutmeg, sage, savine among others) produce symptoms from a direct action on the central nervous system, which is first stimulated and then depressed. The relative importance of these two stages differs in different oils, some, *e. g.*, turpentine oil, causing only a transient excitement followed by marked weakness and depression, while others, such as the oil of absinth, cause very marked excitement and convulsions.

Although these general effects of the volatile oils have no therapeutic importance, the frequent occurrence of epilepsy and insanity in habitual absinth drinkers and occasional poisoning from others of the series have given them some practical interest.

1. Camphor

Some of the volatile oils deposit crystalline substances or stearoptenes after standing for some time, especially when they are exposed to cold. As a general rule these bodies are present in only small amounts, and have not been investigated apart from the volatile oils of which they form constituents; but a few of them have attracted attention in therapeutics, not only on account of their local effects, which resemble those elicited by the volatile oils in general, but also because of their action in the tissues after absorption. The chief of these is Camphor, which has been used in Chinese medicine for many centuries, and which has also played a considerable rôle in Western therapeutics. It is

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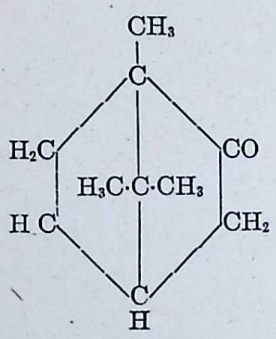
derived from the Cinnamomum camphora of China and Japan, and possesses the formula $C_{10}H_{16}O$, differing from the terpenes in possessing a ketone (=CO) group.

Another body closely resembling ordinary camphor is Borneol or Borneo-camphor ($C_{10}H_{18}O$), which is derived from the Dryobalanops aromatica, and which apparently differs from ordinary camphor in containing the group (=CHOH) instead of (=CO). Nagai-camphor, which is obtained from Blumea balsamifera, is very closely related to borneol. Another stearoptene which has been used in medicine apart from the volatile oils, is **Menthol** ($C_{10}H_{20}O$), which is obtained from the oil of peppermint, and apparently contains a CHOH group like borneol, but is more completely hydrated. **Thujon**, an isomer of camphor occurring in the oil of wormwood or absinth and in many other plants, has not been used in medicine, but is of importance as the cause of epilepsy in chronic absinth drinkers.



Camphor

Local Action.—Camphor is possessed of some antiseptic action, although it is much weaker than some of the bodies of the carbolic acid group, and also than many of the volatile oils. Leucocytes cease their movements at once when exposed to camphor solutions or vapor, and Darwin found that it acts as a stimulus to the tentacles of Drosera, an insectivorous plant, and apparently renders them more sensitive to mechanical irritation.

Camphor produces redness and a feeling of warmth when rubbed into the **Skin**. Sometimes, however, a distinct sensation of cold may be experienced, providing the rubbing is not too energetic. Menthol generally induces this feeling of cold, accompanied by more or less prickling, and afterward by heat and burning. The cold is not due to cooling of the skin, for the vessels of the part are dilated, and the thermometer indicates a higher skin temperature there than in other parts of the body. It has been ascribed to menthol being more irritant to the terminations of certain nerves which convey the sensation of cold than to those of the heat nerves and pain nerves, but this is denied by Rollett who states that menthol acts only on the terminations of the nerves of common sensation or pain. A feeling of numbness and partial anesthesia follows its application after some time.

When taken internally, camphor acts as an irritant and carminative on the mucous membranes like the volatile oils; it has a hot, bitter taste, and in small quantities induces a feeling of warmth and comfort in the stomach, while after large doses nausea and vomiting may be caused by gastric irritation. Some dilatation of the skin vessels follows after it is swallowed, with a sense of warmth; this may probably arise reflexly from the action in the stomach, and is com-

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parable to the dilatation under alcohol and other slight gastric irritants. No other effects follow the use of camphor in therapeutic doses.

When large quantities are taken, they are rapidly absorbed and induce headache, a feeling of warmth, confusion, and excitement in man, with slowing of the pulse and flushing of the skin. This excitement may be shown in hilarity and delirium with hallucinations, in restlessness, or in sudden violent movements, which pass into epileptiform convulsions. These alternate with periods of quiet and unconsciousness, which become longer until the patient sinks into complete stupor. In some cases of poisoning no excitement is observed, the patient falling into a condition of drowsiness, unconsciousness, and stupor immediately. In the lower mammals, camphor induces very similar symptoms, wild excitement and epileptiform convulsions, followed by depression, stupor, collapse, and death from failure of the respiration. Not infrequently, however, the respiration ceases during a convulsion and fails to return when it passes off.

In the frog no excitement is observed except from the local irritation; the animal falls into a condition of depression, in which no spontaneous movements are made, although the reflexes seem to be little affected at first. Later, the reflexes disappear and the animal lies completely paralyzed.

Action: Central Nervous System.—In the frog camphor depresses the brain and later the spinal cord, so that the action is a descending paralysis similar to that seen under chloroform and other anesthetics; thujon often induces violent spasms, which appear to arise from stimulation of the spinal cord and medulla oblongata.

The convulsions in mammals are certainly not due to any action on the spinal cord, but to stimulation of the higher areas of the nervous axis. The cerebral cortex is involved in the action, for the convulsions are less marked on its removal; but in the lower mammals the chief action seems to be exerted on the nervous centers situated between the cerebral peduncles and the medulla oblongata. It is not improbable that in man the cerebral action may be more marked than that on the lower areas, for on descending lower in the scale it is found that the cerebral action becomes less evident; thus in birds the removal of the cerebrum seems to have no effect on the convulsions. The loss of consciousness and the stupor observed in man and the higher animals point to a final paralysis of the cerebral cortex. Later the spinal cord and the medulla are paralyzed and respiration ceases; some observers state that the reflexes of the spinal cord are first augmented by large doses of camphor but others describe depression as the first result.

The **Terminations of the Motor Nerves** are paralyzed in the frog by large doses of camphor, but not in mammals. The **Muscles** are weakened and paralyzed when they are directly exposed to its solutions or vapor.

The **Heart** is sometimes slowed by camphor and its allies in man and animals, but is generally little affected in either strength or rate. It has been stated that the heart has less tendency to pass into fibrillation under camphor, but this is not confirmed. Camphor dilates the coronary vessels but it is not certain that this occurs in man with therapeutic doses. In the frog camphor appears to have some stimulant action on the heart muscle when directly applied to it, but in mammals its effects on the heart in therapeutically possible amounts are trifling or entirely negative.

In mammals, camphor may reduce the **blood-pressure** though there is sometimes a transient rise at first. The slight fall in pressure appears to be due to dilatation of the peripheral vessels through direct action on their walls; the pulmonary vessels share in this dilator action. The vasomotor center is not affected directly by small doses. When sufficient camphor is given to cause convulsions, great variations in the blood-pressure occur, a very marked rise being observed during the convulsive attacks, while in the intervals it falls to below the normal height; these variations appear to arise from a direct action on the vasomotor center, which partakes in the general stimulation. The slight dilation of the vessels is the only change in the circulation observed after camphor, unless when quantities sufficient to cause convulsions are injected.

The **Respiration** is scarcely altered by camphor given in ordinary quantities.

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During the convulsions it is arrested, while in the intervals it may be accelerated from the muscular exertion during the spasms.

The normal **Temperature** is not affected by camphor, but in fever it acts as an antipyretic, like many other aromatic bodies.

Camphor is partially oxidized in the tissues, forming camphorol ($C_{10}H_{16}O_2$), which is **Excreted** in the urine in combination with glycuronic acid, COH-(CHOH)$_4$COOH, and also in part in combination with a nitrogenous body, which is probably uramidoglycuronic acid. Camphorol acts like camphor, but its glycuronic acid combinations are inactive, so that the effects of camphor pass off quickly in such animals as the dog, in which these combinations are rapidly formed.

The action of borneol, menthol, bromated camphor, and camphorol is almost identical with that of camphor itself. Borneol is less irritant locally, and the convulsions are less severe than after camphor, so that animals seldom die during the convulsive stage, and may remain in a state of stupor and collapse for one or two days before the respiration finally ceases. After menthol, the convulsions are even less developed than after borneol. Both of these are excreted in combination with glycuronic acid. Bromated camphor seems to resemble borneol more closely than camphor or menthol, while amido-camphor produces symptoms similar to those of camphor, but is much less powerful. Natural camphor is dextrorotary; the levorotary isomer has been formed recently, and is found to be identical with the natural form in its action.

Therapeutic Uses.—Camphor is used externally in the form of the liniment or spirit as a mild rubefacient in bruises and sprains, and also to destroy parasites. Internally the spirit is prescribed as a carminative.

There is no reason to believe that camphor in even the largest therapeutic doses has any effect after absorption except a slight dilatation of the skin vessels, and it is probable that this also may arise from its gastric effects. Its former uses in hysteria, epilepsy and other nervous disorders, as an aphrodisiac and as an anaphrodisiac were all equally irrational; if any improvement occurred, it was due to hypnotic suggestion and not to the action of the drug.

It has been used in unconsciousness and collapse arising from different causes, in the depression and weakness of acute fevers, and in the most varied forms of failure of the heart and circulation. In many of these cases, improvement in the pulse is said to have been observed; this, like the similar improvement seen after alcohol, may perhaps be explained by its action as a local stomachic irritant producing changes in the circulation reflexly. Solutions of camphor in oil have been injected subcutaneously in these cases. The local irritation produced by the injection may sometimes cause a reflex rise of blood-pressure, and stimulation of the respiration.

Attempts have been made to obtain synthetic compounds which would have a more certain stimulating effect than is possessed by camphor and which would also be soluble in water. The most important members of this group are metrazol and nikethamide. These agents, like camphor, are often referred to as **Analeptics** because of their reputed action in restoring cardiac and respiratory functions. Because of their pharmacological action as **Central Nervous System Stimulants** they are also classified among this group of drugs and since they bear but a slight relationship to camphor pharmacologically they will be considered among the central nervous system stimulants (p. 392).

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Camphor is prescribed in expectorant mixtures, especially in combination with opium, as in paregoric.

Menthol is used almost exclusively for its effects on the sensory nerve terminations, and is a component of many proprietary preparations.

2. Malodorous Volatile Oils

Some of the volatile oils differ from the others in possessing an odor which is disagreeable and nauseating to most people, although not to all. The best known of these are the *Oils of Asafetida* and *Valerian*. The former occurs along with resins and gums exuding from some species of Ferula, and contains several organic sulfur compounds, to which it owes its odor. Oil of Valerian, from Valeriana officinalis, is almost without odor when freshly distilled, but when kept for some time and exposed to the air, it assumes a somewhat unpleasant penetrating odor. It contains two terpenes, borneo-camphor, and numerous esters of formic, acetic and valerianic acid.

Asafetida and valerian were formerly used in hysterical affections, and the benefits accruing from their administration attributed to the mental impression produced by their unpleasant odor and taste, and not to any action they produce after absorption. Asafetida was also used like the ordinary volatile oils as a carminative and as an expectorant, and the emulsion given by the mouth or in an enema to relieve abdominal distention. However, both asafetida and valerian have been dropped from the U. S. Pharmacopeia and might well be discarded from use as relics of an age when the obnoxiousness of a drug rather than its therapeutic value often determined its use in medicine.

Preparations

Aqua Camphoræ (U. S. P., B. P.), camphor water. Dose, B. P., 15 to 30 mil.

Camphora (U. S. P., B. P.) ($C_{10}H_{16}O$), laurel camphor, a stearoptene obtained from Cinnamomum Camphora, or prepared synthetically, forms white translucent, crystalline masses, which are almost insoluble in water but dissolve readily in alcohol, ether, chloroform, fixed and volatile oils. Dose, 0.2 gram.

Linimentum Camphoræ, camphorated oil (U. S. P., B. P.).

Menthol (U. S. P., B. P.) ($C_{10}H_{20}O$), a stearoptene obtained from the oil of peppermint, consists of colorless crystals slightly soluble in water, freely soluble in alcohol or ether. Dose, B. P., 0.03 to 0.12 gram.

Spiritus Camphoræ (U. S. P., B. P.), spirit of camphor. Dose, U. S. P., 1 cc.; B. P., 0.3 to 2 mil.

Tinctura Opii Camphorata (U. S. P., B. P.), paregoric. Dose, U. S. P., 4 cc.; B. P., 2 to 4 mil.

Tinctura Opii Camphorata Concentrata (B. P.), concentrated camphorated tincture of opium, Liquor Opii Camphoratus Concentratus, concentrated camphorated solution of opium. Dose, 0.25 to 0.5 mil.

Terpineol (B. P.), terpineol, $C_{10}H_{18}O$.

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IV. DRUGS AFFECTING TASTE

1. Sugar

Sugars are used in medicine chiefly to disguise preparations of unpleasant taste, and in the small quantities usually employed have little further effect. In large quantities sugars, like other diffusible bodies, act as irritants to the stomach and bowel, and comparatively small quantities of some sugar substances possess an aperient action; this seems to be due to their colloid form, as pure sugar has no such effect, and it is possible that they merely delay the absorption of fluid, and thus cause softer evacuations than would otherwise occur.

PREPARATIONS

SUCROSUM (U. S. P., B. P.), $C_{12}H_{22}O_{11}$, refined cane sugar.

SYRUPUS (U. S. P., B. P.), a concentrated solution of sugar. Syrup is the basis of a large number of medicated syrups of the pharmacopeias. Sugar and syrup are used exclusively to sweeten mixtures and to aid in the suspension of insoluble bodies. In place of ordinary syrup many of the flavored preparations may be used, such as the syrups of citric acid, acacia, almonds, or of the volatile oil group.

LACTOSUM (U. S. P., B. P.), $C_{12}H_{22}O_{11}.H_2O$; sugar of milk, lactose, is not so sweet as ordinary sugar, and is much less liable to deliquesce, so that it is used largely to give bulk to powders.

LÆVULOSUM (B. P.), fructose, consists chiefly of levulose ($C_6H_{12}O_6$) with small quantities of dextrose. It has greater sweetening power than cane sugar.

DEXTROSUM (U. S. P., B. P.), $C_6H_{12}O_6$, dextrose, also known as glucose, is a sugar usually obtained by the hydrolysis of starch. Glucose is a food which is readily absorbed and is given in debilitating diseases, when the intake of food that can be digested is insufficient. A liver rich in glycogen resists the action of toxic agents better than one poor in glycogen, and hence glucose is given to prevent damage to the liver from chloroform, cinchophen or other liver poisons. Solutions of glucose are often given by intravenous injection in cases of acute circulatory failure, such as may occur in infectious diseases or in case of shock or hemorrhage, to supply fluid. It is usually given in a 5 or 10 per cent solution, the former concentration being approximately isotonic with blood. It may also be given in the form of an enema. Pure dextrose must always be used for such injections.

Dextrosum is a white crystalline powder and must not be confused with liquid glucose, GLUCOSUM LIQUIDUM (U. S. P., B. P.). The latter is a viscid, syrupy liquid containing a mixture of dextrose, maltose, dextrin and water, and is chiefly used for its physical properties as a pill excipient. It cannot be used for intravenous injection, etc.

EXTRACTUM MALTI (U. S. P., B. P.), extract of malt, is a brownish viscous liquid with a sweetish taste. It contains nutritive carbohydrates and also usually diastatic ferments capable of converting starch into sugar. It forms a good vehicle for giving cod-liver oil, as in the B. P. EXTRACTUM MALTI CUM OLEO MORRHUÆ.

MEL (U. S. P.), MEL DEPURATUM (B. P.), clarified honey, is used to give taste to mixtures, and has a very slight aperient action.

A number of saccharine preparations with a slight aperient effect are ingredients of the preparations of the more powerful purgatives. Thus purging Cassia (CASSIA, B. P.), tamarinds (TAMARINDUS, B. P.), figs and prunes form constituents of the Confection of Senna and other preparations. They are not prescribed alone, but the fruits may be advised as articles of diet where a mild laxative is required. The tamarind pulp may owe its aperient action in part to the presence of tartrates, citrates, malates, and other cathartic salts. (See Saline Cathartics.)

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2. Flavoring Extracts

Frequently other flavors are preferred to sugar, which is especially disliked in fever cases, as sweet fluids do not quench the thirst so effectually as acids and bitters. Many of the preparations of the volatile oils and some of the demulcents are used almost exclusively as flavoring agents, and in some both sugar and volatile oil are combined, as in the syrups.

Instead of sugar some artificial compounds have been introduced of late years. Saccharin (U. S. P.), $C_6H^4\langle{}^{CO}_{SO_2}\rangle NH$, and its sodium salt (*Saccharinum sodicum*, U. S. P., *Saccharinum Soluble*, B. P.), $C_6H_4\langle{}^{CO}_{SO_2}\rangle NNa$, or soluble saccharin, are the best known of these. Saccharin is a light, white, crystalline powder, soluble in 400 parts of water and in 25 parts of alcohol. It is about 500 times as sweet as sugar, and gives a distinct flavor to 70,000 times its weight of water. It does not taste exactly like sugar, however, there being a distinct flavor besides that of sweetness, and patients generally object to it after a short time. It has been used as a substitute for sugar in diabetes and in the obese since it has, of course, no food value. Saccharin in ordinary amounts has no deleterious action on the digestion or after absorption.

Some pharmacopeial preparations are designed to give color to solutions, but are seldom or never prescribed, although they are sometimes added by the pharmacist.

Among these are cochineal (*Coccus*, U. S. P., B. P., *Tinctura Cocci*, B. P.) and saffron.

3. Volatile Oils Used as Flavoring Agents and Carminatives

Many plants depend for their odor and taste upon the presence of volatile oils and these have been employed from earliest times to give flavor to medicinal preparations. One oil is used by one physician, another by another, and the selection is largely a matter of custom and taste. Some volatile oils are used as carminatives (p. 208) when no marked irritation of the stomach or intestine is present. In cases of colic, flatulence and abdominal distention they are often of use, provided that these are not due to peritonitis and other inflammatory diseases. Several of them have been employed as surgical antiseptics, but they are more widely used as parasiticides for scabies, pediculi, etc. Some of the oils, such as oil of cloves, are used in dentistry to relieve pain by paralyzing the exposed nerve ends after a preliminary irritation. Some of them, particularly thymol, have been used as anthelmintics but have been replaced by less toxic and more effective drugs. Externally some of them are used as mild skin-irritants, generally in the form of spirits. Arnica once had a popular reputation as a stimulating local remedy in bruises and sprains.

The volatile oils are largely used as flavors in cookery and sweetmaking, and are important constituents of many of the popular liqueurs, and therefore have a certain dietetic importance.

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PREPARATIONS

CRUDE DRUGS.—Many of the pharmacopeial preparations are whole plants, seeds, leaves, or flowers, and are never prescribed, although some of them are used in popular medicine in the forms of infusions or "teas." The virtues of these old-fashioned remedies lie perhaps more in the large draughts of warm water than in the traces of volatile oil which they contain, but the presence of the latter prevents, to some extent, the nausea produced by warm water alone. These infusions are used to induce perspiration in fevers or chills, as diuretics, or to relieve colic and griping, and generally contain about a tablespoonful of the herb to one or two cupfuls of water. The most frequently used for this purpose are peppermint and spearmint leaves and tops (MENTHA PIPERITA and MENTHA VIRIDIS, U. S. P.); Coriander seeds (CORIANDRUM, B. P.); Chamomile flowers; Anise, the fruit of Pimpinella anisum; Elderflower and Horehound. In different countries, however, the constituents of the herbalist recipes vary according to the local flora. The U. S. and B. Pharmacopeias recognize a number of other crude drugs of this group which need only be enumerated here: AURANTII AMARI CORTEX (bitter orange peel), CARYOPHYLLUM (cloves), CINNAMOMUM (cinnamon), CARDAMOMUM (cardamom), CARUM (caraway), MYRISTICA (nutmeg), and ZINGIBER (ginger).

PRUNUS VIRGINIANA (U. S. P.), PRUNUS SEROTINA (B. P.), contains amygdalin or some nearly related substance, and emulsin, and forms benzaldehyde and prussic acid when rubbed up with water. The SYRUPUS (U. S. P., B. P.) is frequently used as a flavoring agent and in cough mixtures.

The VOLATILE OILS themselves are also represented in unnecessarily large numbers in the pharmacopeias.

U. S. P.—OLEUM MENTHÆ PIPERITÆ (oil of peppermint), OL. MENTHÆ VIRIDIS (spearmint), OL. LAVANDULÆ (lavender), OL. EUCALYPTI (eucalyptus), OL. LIMONIS (lemon), OL. AURANTII (orange), OLEORESINA ZINGIBERIS (ginger), OL. AMYGDALÆ AMARÆ (bitter almonds), OL. CARYOPHYLLI (cloves), OL. CINNAMOMI, OL. CORIANDRI (coriander), OL. SASSAFRAS (sassafras), OL. ANISI (anise), OL. FŒNICULI (fennel), OL. ROSÆ, OL. ROSMARINI (rosemary), OL. JUNIPERI (juniper), OL. MYRISTICÆ (nutmeg).

B. P.—OLEUM ANETHI (oil of dill), OL. ANISI (anise), OL. CAJUPUTI (cajuput), OL. CARI (caraway), OL. CARYOPHYLLI (cloves), OL. CINNAMOMI (cinnamon), OL. CORIANDRI (coriander), OL. EUCALYPTI (eucalyptus), OL. LAVANDULÆ (lavender), OL. LIMONIS (lemon), OL. MENTHÆ PIPERITÆ (peppermint), OL. MYRISTICÆ (nutmeg), OL. ROSMARINI (rosemary), OL. AMYGDALÆ (bitter almond).

The majority of these oils resemble each other very closely in their effects and require no special comment. The oils of rosemary, juniper, and savine are more irritant than the others, and are seldom used. The oils of wintergreen and of birch consist mainly of methyl salicylate, and may be used instead of the other salicylates. Nutmeg and mace oils are more poisonous than the others, not from their local irritant action so much as from their effects after absorption.

The volatile oils themselves are comparatively little used. A single drop may be added to powders, pills or solutions to give a pleasant odor.

Spiritus are formed from many of the volatile oils by dissolving them in alcohol, sometimes with the addition of water and sometimes with some of the crude drugs, so that the preparation is really a mixture of tincture and spirit. The spirits or essences of the volatile oils are used very largely as flavoring agents in mixtures for internal use, and are often added to external applications to lend them odor. They may also be prescribed where alcohol is indicated but is distasteful to the patient; the spirits of the volatile oils contain 80 per cent or more of alcohol, and have to be diluted accordingly. Any of them may be

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used as carminatives, but the spirits of peppermint, cinnamon, anise and lavender are more frequently used for this purpose than the others. Another useful carminative preparation is camphorated tincture of opium, which contains camphor and several volatile oils along with a small amount of opium; the last aids the real carminative in relieving the discomfort by its action after absorption.

U. S. P.—Spir. Anisi, Spir. Aurantii Compositus (containing the oils of orange peel, lemon, coriander, and anise), Spir. Cinnamomi, Spir. Lavandulæ, Spir. Menthæ Piperitæ, Spir. Menthæ Viridis.

Elixir Aromaticum is a preparation of the Spir. Aurantii Compositus used as flavor.

B. P.—Spiritus Cajuputi, Sp. Menthæ Piperitæ.

Aquæ.—The volatile oils are very insoluble in water, but when they are shaken in it, enough remains in the water to give it the odor and taste of the oil. In the process of obtaining the oils from the crude drugs by distillation, some oil is held by the water, and a number of these waters (aquæ) are contained in the pharmacopeias. They are used as substitutes for distilled water in making up prescriptions, the small quantity of volatile oil serving merely to give a pleasant odor and taste.

The aromatic waters of the U. S. P. are made either by distillation of the appropriate part of the plant or by solution of the volatile oil in water. The B. P. contains some prepared by distillation (Aquæ Destillatæ) and others made by simple solution of the essential oil. It also contains a few Aquæ Concentratæ (*e. g.*, Aqua Cinnamomi Concentrata) which, on dilution with thirty-nine times their volume of distilled water, yield preparations approximately equivalent in strength to the distilled waters.

U. S. P.—Aqua Anisi, Aq. Aurantii Flor., Aq. Cinnamomi, Aq. Fœniculi, Aq. Menthæ Piperitæ, Aq. Menthæ Viridis, Aq. Rosæ, Aq. Rosæ Fortior (the latter twice as strong as the other).

B. P.—Aqua Anethi Destillata, Aq. Anisi Destillata, Aq. Cinnamomi Destillata, Aq. Menthæ Piperitæ Destillata. Each of these has a corresponding concentrated water.

Some of the preparations containing volatile oils are derived not from the oil itself, but from the crude drug, and therefore contain non-volatile substances which are generally absent from the preparations already mentioned. As a general rule these non-volatile bodies are inactive, but in some cases, bitters or resins are contained in the preparations, and may influence their action. Thus a bitter glucoside, hesperidin, is found in the orange peel, and is present in the preparations formed directly from it, while it is absent from those formed from the volatile oil. Ginger contains a resin of hot, burning taste, which increases the carminative action of the oil. Cinnamon contains some tannic acid, which passes over in the tincture, while a fixed oil is contained in cardamom.

Among the preparations formed from the crude drugs are the **Syrups**, which are used exclusively as flavoring agents.

U. S. P.—Syrupus Aurantii Florum, Syr. Aurantii, Syr. Pruni Virginianæ, Syr. Balsami Tolutani.

B. P.—Syrupus Aurantii, Syr. Limonis, Syr. Pruni Serotinæ, Syr. Zingiberis, Syr. Tolutanus.

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The **Tinctures** are used for the same purposes as the spirits of the pure oils.

U. S. P.—TINCT. AURANTII AMARI, TINCT. AURANTII DULCIS, TINCT. LIMONIS, TINCT. CARDAMOMI COMPOSITA (containing cardamom, cinnamon, caraway), TINCT. LAVANDULÆ COMPOSITA (oils of lavender, rosemary, cinnamon, cloves, nutmeg).

B. P.—TINCT. AURANTII, TINCT. CARDAMOMI COMPOSITA (containing cardamom, caraway, cinnamon), TINCT. CINNAMOMI, TINCT. LIMONIS, TINCT. ZINGIBERIS MITIS, 2 to 4 mil. (30 to 60 min.), and TINCTURA ZINGIBERIS FORTIS (Essence of Ginger).

FLUIDEXTRACTS of the volatile oil series.

U. S. P.—FLUIDEXTRACTUM ZINGIBERIS. Dose, 0.6 cc.

PURE PRINCIPLES used as flavors:

VANILLINUM (U. S. P.), vanillin ($C_6H_3 \cdot OH \cdot OCH_3 \cdot COH$), occurs in vanilla and is also made synthetically. It forms white needle crystals, slightly soluble in water, easily soluble in alcohol and ether, and possesses the odor and taste of vanilla.

EUGENOL (U. S. P.), a phenol ($C_6H_3OH \cdot OCH_3 \cdot C_3H_5$) obtained from oil of cloves and other oils, and forming a colorless liquid with an odor like cloves and a hot, burning taste.

These principles are used chiefly to give flavor and color.

4. Simple Bitters

This group includes a number of substances which have little in common except their bitter taste and their comparative inactivity in the body. Several alkaloids may be placed in it, *Berberine, Buxine, Menispermine* and *Canadine,* for, although these are poisonous in very large quantities, they are harmless in those in which they are contained in the preparations used in therapeutics. In addition to these there may be placed in it numerous neutral bodies, possessing an intensely bitter taste, but with little or no further action, such as the *Quassiins, Calumbin,* and a few weak acids and glucosides.

Pharmacological Action.—Preparations containing bitters were formerly largely used in therapeutics in order to increase the appetite. They are used infrequently now having been replaced for the most part by the vitamin preparations which are now used as indiscriminately as were formerly the bitters. The effects of the bitters on appetite are explained by the action of bitter substances in increasing the secretion of gastric juice, which has been shown to occur in man and animals by a number of experiments. This is not, however, through the bitters acting on the gastric mucous membrane directly, for when they are applied through a gastric fistula, they have no specific action on the secretion. Pawlow has shown that the chief factor that determines the activity of the gastric secretion is the odor and taste of food; thus in dogs with esophageal fistulæ, in which the food swallowed does not pass into the stomach but escapes through a wound in the esophagus, the taste and odor of food cause a profuse secretion of gastric juice (psychical secretion). Bitters given shortly before a meal sometimes augment this reflex in normal animals but this is more distinct and occurs more often when cachexia is present; this is due to action in the

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mouth only, for it is seen when the bitter is not swallowed, and is absent when it is passed into the stomach through a fistula. This change in the secretion is accompanied by improved appetite in cachexia, while the hunger contractions of the stomach are arrested by bitter tastes; introduced directly into the stomach, the bitters have little or no effect in therapeutic doses. The action of the bitters is therefore to increase the psychical secretion of gastric juice, possibly because of the contrast offered by the bitter and the pleasant tastes. The inference may be drawn that the therapeutic effects are best elicited when the bitters are given shortly before a meal, and this accords with universal experience. In addition, it is to be remembered that the improvement is largely subjective, and that the bitters are capable of producing a considerable impression upon patients, so that the effects may be due to suggestion and not to any real action of the drug. The same is true of the use of vitamin preparations where no actual avitaminosis exists.

Instead of the simple bitters, cinchona and nux vomica preparations are often used in small quantities. Many of the preparations which will be enumerated under the volatile oil series owe much of their effect to the bitter which accompanies the volatile oil, and in numerous other pharmacopeial preparations bitters are present, although their effect is hidden by the action of the drug in other directions.

Therapeutic Uses.—The bitters are used chiefly to increase the appetite and the digestion. In cases of gastric irritability and in hyperacidity they may do harm rather than good. Gentian, Quassia and Calumba are the only simple bitters that are largely used, and the first is much the most important. They are generally prescribed as tinctures, infusions or other fluid preparations. The last two may be prescribed with iron preparations, as they contain little or no tannic acid and thus cause no precipitate. Pills are sometimes prescribed with extract of gentian which has little, if any, effect when given in this form, as the bitter taste, on which its action depends, is largely concealed. Compound tincture of gentian is sometimes used to give flavor rather than for any effect on the digestion. Quassia infusion (10 per cent) is injected as an enema in the round worms of children.

Preparations

Calumba (B. P.), calumbo, the root of Jateorrhiza palmata, or Calumba, contains calumbin, a neutral body, calumbic acid, and three alkaloids, calumbamine, jateorrhizine, and palmitine, closely resembling berberine.

Extractum Gentianæ (B. P.).

Gentiana (U. S. P., B. P.), gentian, the root of Gentiana lutea, contains a glucoside, gentiopicrin, and a trace of tannic acid.

Infusum Calumbæ Concentratum (B. P.). Dose, 2 to 4 mil.

Infusum Calumbæ Recens (B. P.). Dose, 15 to 30 mil.

Infusum Quassiæ Recens (B. P.). Dose, 15 to 30 mil.

Quassia (B. P.), the wood of Picrasma excelsa or of Quassia amara, contains several neutral bitter substances, resembling each other closely chemically and known as quassins. Dose, 0.12 to 0.5 gram.

Tinctura Aurantii Concentrata (B. P.), concentrated tincture of orange. Dose, 0.5 to 1 mil.

Tinctura Calumbæ (B. P.). Dose, 2 to 4 mil.

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TINCTURA CARDAMOMI COMPOSITA CONCENTRATA (B. P.), concentrated compound tincture of cardamom. Dose, 0.5 to 1 mil.

TINCTURA GENTIANÆ COMPOSITA (U. S. P., B. P.), containing gentian, bitter orange peel, and cardamom. Dose, U. S. P., 4 cc.; B. P., 2 to 4 mil.

TINCTURA GENTIANÆ COMPOSITA CONCENTRATA (B. P.), concentrated compound tincture of gentian. Dose, 0.5 to 1 mil.

TINCTURA LIMONIS CONCENTRATA (B. P.), concentrated tincture of lemon. Dose, 0.5 to 1 mil.

TINCTURA QUASSIÆ (B. P.). Dose, 2 to 4 mil.

TINCTURA QUASSIÆ CONCENTRATA (B. P.), concentrated tincture of quassia. Dose, 0.5 to 1 mil.

5. Pepper Group

The pepper group comprises a few drugs which are used for their effect on digestion but which have a much more pungent taste than the bitters, and cause marked irritation when they are applied in large doses. They thus stand midway between the simple bitters and the carminative volatile oils, and are sometimes known as aromatic stomachics.

Black Pepper contains a weakly basic substance, *Piperine* (which is broken up by caustic alkalies into *Piperidine* and *Piperinic acid*), in addition to a volatile oil and a bitter pungent resin. Piperine is insoluble in water, and has therefore no taste when absolutely pure, but is hot and pungent to the taste when it is taken in solution.

Pyrethrum, or pellitory, contains similar constituents but is scarcely used except as an ingredient of insect powders.

Capsicum, or Cayenne pepper, contains *Capsaicin*, a neutral body with a hot pungent taste.

Pepper and capsicum are largely used as condiments, and are comparatively seldom prescribed in therapeutics. *Unguentum Capsici* (B. P.) is used as a rubefacient. *Tinctura Capsici* (B. P.), 0.3 to 1 mil., and *Tinctura Capsici Concentrata* (B. P.), 0.06 to 0.25 mil., are sometimes used as stomachics and have been employed in chronic alcoholism in order to provide a substitute for the local irritant effects of spirits in the stomach.

Piper Methisticum, or Kava Kava, is used in the South Sea Islands to prepare an intoxicating liquor.

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V. DIGESTIVE FERMENTS

A number of digestive ferments have been introduced into therapeutics for the treatment of gastric and intestinal disorders. The earlier members of the series were proteolytic ferments, intended to reinforce the pepsin of the stomach, but of recent years the amylolytic ferments have also been strongly advocated.

1. Pepsin

The pharmacopeial preparations of pepsin are generally obtained from the pig's stomach. It digests only in acid solution, the best results being obtained in a solution of 0.2 per cent of hydrochloric acid. In alkaline solution it is inert, and in fact is rapidly decomposed, so that

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when pepsin and alkaline carbonates or bicarbonates are prescribed together, the effects are due to the alkalies only.

Pepsin is used in therapeutics on the theory that the stomach does not secrete enough of the ferment in certain conditions. But it may be questioned whether this is true in even a small proportion of the cases treated with pepsin, for the gastric juice is almost always capable of digesting proteins if it is acid in reaction. In a number of forms of dyspepsia the acid secretion is insufficient, but the ferment is almost always present in quantity, for it digests proteins outside the body as soon as it is acidulated. On the other hand, the administration of hydrochloric acid tends to diminish gastric secretion; hence, in cases of defective gastric secretion, better results may be obtained if pepsin is added when acid is given by the mouth.

2. Pancreatic Ferments

The pancreatic ferments have also been introduced into therapeutics, generally in the form of an extract of the gland, *pancreatin*. These ferments differ from pepsin in acting only in alkaline or neutral solution, and besides digesting proteins, form sugar from starch and saponify and emulsify fats. The pancreatic ferments are rendered inert by a comparatively short exposure to the acid gastric juice.

The value of pancreatin is even more problematical than that of pepsin, for though it would no doubt be valuable where the digestive ferments, particularly those of the pancreas, were deficient, this has not been shown to occur. On the other hand, the pancreatic ferments are certainly destroyed in passing through the stomach. It has been suggested, however, that they may act in the stomach, if they are given before or with the food, as the acid gastric juice is only secreted slowly, and some time must elapse before the pancreatin is rendered inert. Attempts have been made to preserve the pancreatin from the deleterious effects of the gastric juice by administering it in capsules which are dissolved only in the intestine. It is certainly possible that the pancreatin may be useful in rare cases, where the ferments of the pancreas are absent and the acid of the stomach so deficient as not to be destructive.

PREPARATIONS

PANCREATINUM (U. S. P., B. P.), a mixture of the enzymes naturally existing in the pancreas of warm-blooded animals, usually obtained from the fresh pancreas of the pig. It forms a yellowish, yellowish-white, or grayish, amorphous powder, having a faint, not disagreeable odor and a meat-like taste, and is slowly soluble in water. U. S. P., 0.5 gram, in powder or in capsules. B. P., 0.2 to 0.6 gram.

3. Vegetable Ferments

Besides these animal digestive ferments, a number of vegetable proteolytic enzymes are known, and have enjoyed a more or less short-lived popularity. Probably many more plant juices are able to digest proteins than are at present generally recognized; thus many of the bacteria liquefy gelatin and albumin, and the insectivorous plants, such as *Drosera* (sundew) and *Dionea*, secrete a digestive fluid. Figs, pineapple (*bromelin*), the scarlet pimpernel (*Anagallis arvensis*), and many others of the higher plants have been shown to possess

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these ferments, but the best known of these is the carica papaya, or pawpaw, which contains a digestive ferment known as *papain*. This ferment acts in neutral, slightly acid, or alkaline solution at the temperature of the body and in the cold. It has been used instead of pancreatin and pepsin in disorders of the digestion, and also as an anthelmintic.

4. Diastase

Several amylolytic or sugar-forming ferments have been used more or less in therapeutics, the first of these being the *diastase* or *enzyme of malt*, which is known under the names of malt extract, or maltzyme. When grain is allowed to germinate, its starch is formed into a soluble form (sugar) by means of a ferment known as diastase, and it was supposed that this diastase might aid the digestion of starchy foods in the body. When malt extract is formed at a low temperature, it unquestionably contains diastase and is capable of digesting starch, but many of the extracts on the market are quite inert, the ferment having been destroyed by heat. Those extracts are therefore devoid of digestive power, but form a pleasant, easily digested food. More recently some other sugar-forming ferments have been brought forward, notably *Taka-diastase* obtained from *Eurotium oryzæ*, a mould of the aspergillus family; it has been recommended in cases in which there is supposed to be a deficient digestion of starch. It ceases to act in the gastric juice as soon as the acidity exceeds 0.1 per cent, but may be able to digest a certain amount of starch in the mouth and stomach before it is destroyed. Until it is shown that in some cases the digestion of starch by the intestinal ferments is insufficiently performed, the diastase preparations should seem to be superfluous.

5. Bile and Bile Salts

The bile performs an important function in the digestion of fats, in the activation of the pancreatic enzymes and indirectly in the absorption of the fat soluble vitamins (A, D, E, and K) and calcium. In addition bile exerts a slight antiseptic and laxative action. The active principles of bile which are responsible for its action are the bile salts. These consist of combinations of taurine (amino-ethylsulfonic acid) and glycine (amino-acetic acid) with cholic acid and related bile acids. The bile salts are produced in the liver and by their emulsifying action on the fats make possible their digestion. The bile salts also stimulate the secretion of both the water and solid constituents of the bile by the parenchymal cells of the liver and are therefore designated as **Choleretics.** The choleretics are to be distinguished from the **Cholagogues** which stimulate evacuation of the gall bladder. Substances which increase the volume of the bile alone without affecting its solid constituents are designated as hydrocholeretics.

In addition to the bile salts, bile contains the bile pigments derived from the breakdown of hemoglobin, cholesterol, lecithin and inorganic salts, but it is only the bile salts which are physiologically important.

In addition to preparations of bile salts prepared from fresh ox bile, certain other derivatives of bile acids have been used as choleretics.

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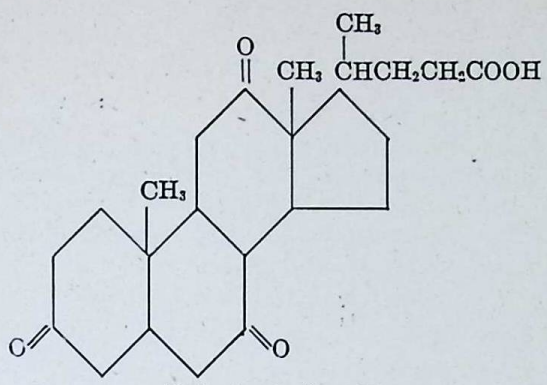
Of these the most important is dehydrocholic acid which is obtained by oxidizing cholic acid.



Dehydrocholic acid

Bile given by the mouth does not cause any symptoms except those from the intestine and liver. When it or purified bile salts are injected into the blood, however, they depress the central nervous system and the heart muscle by direct action on these organs, and dissolve the red cells of the blood in the same way as do the saponins which they resemble in reducing surface tension. Muscles and nerves suspended in a solution of bile salts rapidly lose their irritability, and some unicellular organisms are killed and dissolved by them. Bile itself is not so toxic as an equivalent quantity of bile acids, due doubtless to the presence in the bile of protective substances (cholesterol). The injection of toxic amounts of bile acids into dogs produces an increased rate of the respiration and a profound fall in blood-pressure.

Therapeutic Uses.—The bile salts are used in medicine primarily as a substitution therapy in nutritional disturbances where there is a deficiency of these salts in the intestine. Where there is evidence of a deficiency of bile with resulting interference with the digestion of fats, the addition of bile salts is indicated. Dehydrocholic acid is used principally for its action in increasing the volume of bile formation (*i. e.*, for its hydrocholeretic action). Its choleretic action is uncertain. It is used where it is desired to increase the drainage of the bile ducts and to discourage the ascent of infection as in cholecystitis, non-calculous cholangitis and other conditions involving biliary stasis. The bile salts and dehydrocholic acid are administered in doses of 0.25 to 0.5 gram two to three times daily after meals.

The sodium salt of dehydrocholic acid is also used in the determination of the arm to tongue circulation time as a diagnostic aid in conditions affecting the velocity of the blood flow. For this purpose 3 to 5 cc. of a 20 per cent aqueous solution are rapidly injected into the cubital vein and the time noted when a bitter taste is experienced by the patient. The use of sodium dehydrocholate is contraindicated in patients suffering from bronchial asthma.

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PREPARATIONS

U. S. P.

FEL BOVIS, ox gall, is the fresh bile of the ox.

EXTRACTUM FELLIS BOVIS. One gram of the powdered extract of ox gall represents 8 grams of fresh ox gall. Dose, 0.3 gram.

B. P.

EXTRACTUM FELLIS BOVINI, purified ox bile, is prepared from fresh ox bile and contains the bile salts and pigments. Dose, 0.3 to 1 gram.

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VI. VEGETABLE ASTRINGENTS—TANNIC ACID SERIES

A large number of vegetable substances owe their action to their containing tannin substances, while in many other preparations the effect of more important constituents is modified by the presence of these widely distributed bodies. The tannins are naturally occurring derivatives of polyhydroxybenzoic acids. Tannic acid proper is a feebly acid substance derived from the oak gall, and is a compound of gallic acid (trihydroxybenzoic acid) into which it is easily decomposed. The tannins possess a number of reactions in common and are generally classed together as the tannic acid substances. They precipitate albumins, gelatin, alkaloids and some glucosides, and the salts of the heavy metals. The salts of iron form a bluish-black or greenish-black precipitate.

Action.—The pharmacological effects of these bodies are due to their precipitating albumins and other proteins. If tannic acid solution is added to a neutral or weakly acid solution of albumin, peptone, or gelatin, a white precipitate forms, which is entirely insoluble in water, but is soluble in excess of albumin or gelatin, in stronger acid, and in alkaline solutions. This protein tannate, exposed to the action of the gastric juice, undergoes digestion and is dissolved in the same way as an ordinary coagulated protein such as fibrin. During the process, the tannic acid is set free from its combination and if it reaches a position in which the reaction is nearly neutral, it can again precipitate proteins. Strong alkali prevents the precipitation and the so-called tannates of the alkalies are thus devoid of this action.

Tannic acid applied to animal tissue, as in the tanning of leather, causes a precipitation of the proteins, and the tissue becomes harder and tougher and tends to shrink together; at the same time it has less tendency to undergo putrefactive changes and does not lose its flexibility, as it would in drying. Applied to a living mucous membrane, which is neither strongly acid nor alkaline, a dilute tannin solution pre-

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cipitates a fine pellicle of mucus and protein, which protects the cells beneath and lessens their sensitiveness to external stimuli. A stronger solution may cause some precipitation in the cells themselves and thus injure them and cause irritation.

Tannic acid solutions have a harsh, bitter, "astringent" taste, and produce in the mouth a feeling of constriction, dryness and roughness, along with a sense of stiffness in the movements of the tongue, and some loss of taste. These effects are due to the coagulation of the superficial layers of protein, which substitutes for the ordinary smooth surface a firmer, less even one over which the tongue can no longer move easily. The feeling of constriction may, perhaps, be caused by an actual shrinking of the superficial layers of the epithelium, or may be due merely to the impaired movements and sensation.

The astringent feeling is continued in the throat as the solution is swallowed, and occasionally some irritation or even nausea and vomiting are provoked by it, but as a general rule, no such effects are observed. The stools are rendered harder and firmer by the administration of tannic acid, and constipation is often produced by it. In excess, tannic acid sometimes causes irritation of the intestine and diarrhea, but beyond these symptoms of local irritation of the stomach and bowel, no effects arise even from enormous quantities of the drug.

In the resting stomach, tannic acid combines with any protein substance with which it may come in contact and precipitates it, but as digestion progresses and the reaction becomes more strongly acid, this combination is broken up. In the intestine, the reaction becoming again less acid, tannic acid causes the same superficial precipitation as in the mouth, and the pellicle of precipitated protein acts as a protective to the mucous membrane. The contents thus have less effect in starting the peristaltic reflex and the movements are retarded, so that there is longer time for the absorption of the fluid part of the contents. The secretion of mucus by the intestinal epithelium is also lessened and this may also retard the passage of the contents, which therefore become drier and harder.

The local application of tannic acid causes a diminution of the secretions of the skin glands. This is due to its effects upon the protoplasm of the secreting cells, which probably undergoes the initial stages of coagulation. In acting as a protective to mucous surfaces, tannic acid may reduce congestion but there is no reason to suppose that it acts more directly on the vessel walls or, in fact, that it ever reaches them in an active form. In the same way it may indirectly lessen the inflammatory exudation from the vessels and the leukocytosis.

When tannic acid is taken internally, a small proportion is sometimes eliminated by the bowel unchanged, but very often none is to be found in the stools; traces are apparently absorbed and excreted in the urine. But much the greater part of the tannic acid is decomposed in the intestine into gallic acid, some of which often passes out in the stools, some in the urine. Only about 1 per cent of the tannic acid swallowed reappears in the excretions, either as tannic or gallic acid; the rest apparently undergoes complete oxidation, for no further trace of it can be found.

Tannic acid then does not exist in the tissues as such, but only in the form of traces of the gallate or tannate of sodium, which are so small as to be devoid of astringent properties. The effects of tannic acid are therefore limited to the point of application, and it exercises no action after absorption. The alkaline tannates are generally believed to be entirely devoid of astringent effects, but the tannic acid is freed to some extent by such feeble acids as carbonic acid, so that the astringent action is present in the intestine.

Therapeutic Uses.—The preparations of tannic acid are used for their local effects exclusively. They are applied externally in cases of exces-

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sive secretion, as in local sweating or weeping ulcers, and occasionally to harden the skin. For this purpose tannic acid may be used in solution in water, or in the form of the glycerite or ointment, or some other fluid preparation may be preferred. Tannic acid is used as an astringent mouth wash and may be prescribed in a flavored solution or in the form of lozenges of which the pharmacopeia offers a choice. In certain forms of diarrhea the astringent action of tannic acid is of considerable value, and occasionally when such drugs as cod-liver oil cause diarrhea, tannic acid prevents this action without hindering their general effects. The pure drug is seldom used in these cases, as it is liable to derange the stomach and to form compounds with the albumins before it reaches the bowel, and catechu, krameria or kino may be prescribed, either in the form of pills or in fluid preparations. An old preparation was the compound kino powder, which combined the astringent action of tannin with the specific action of opium on the intestine. Recently the preparations mentioned above have been largely replaced by some of the newer synthetic compounds such as acetyltannic acid or the tannate of albumin. In these and similar compounds the tannic acid is in a relatively firm combination with the rest of the molecule. Accordingly it is not freed in the stomach, the compound having to pass into the intestine before it is broken up, releasing the tannic acid. Tannic acid stops hemorrhage by precipitating the proteins when it comes into immediate contact with the bleeding point, but it is not of so much value for this purpose as epinephrine or some of the metallic astringents.

Tannic acid has assumed an important rôle in the treatment of burns since its introduction for this purpose by Davidson in 1925. The rationale of its use is dependent on the fact that by coagulating the surface of the wound the formation and absorption of toxins resulting from bacteria, as well as from tissue disintegration, are prevented. A 20 per cent solution of tannic acid in which antiseptics (silver nitrate or dyes) may be incorporated are sprayed on the denuded area after cleansing and removing the devitalized epidermis. The formation of a rigid eschar reduces the primary shock which is largely due to the escape of fluid from the burned area. The blood becomes concentrated and there is loss of fluid and electrolytes. The coagulation of the surface by tannic acid lessens the loss of fluid. An important part of the constitutional treatment is the administration of blood and plasma.

Tannic acid is not itself a direct antiseptic unless perhaps the strength is at least 10 per cent, and in deep burns, sepsis may occur under or at the edge of the coagulum. To lessen or prevent this, various additional antiseptics have been recommended, *e. g.*, silver nitrate, 1 in 1000 acriflavine, or 1 in 100 gentian violet. The newer chemotherapeutic agents (sulfonamides and antibiotics) combined with pressure bandages, and transfusions to prevent shock have to a great extent replaced the tannic acid method of treating burns.

In cases of poisoning with metals and alkaloids, tannic acid is often used to cause their precipitation in the stomach, but the tannate formed must be removed at once, as it is gradually dissolved in the digestive

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fluids. The administration of tannic acid is therefore only a temporary expedient to allow of active measures being taken to empty the stomach.

Some individuals are peculiarly susceptible to the action of tannic acid, which induces local irritation and inflammation wherever it is applied in these cases.

PREPARATIONS

U. S. P.

ACIDIUM TANNICUM, tannic acid.
GLYCERITUM ACIDI TANNICI, 20 per cent tannic acid.
UNGUENTUM ACIDI TANNICI contains 20 per cent tannic acid.

B. P.

ACIDUM TANNICUM.
GLYCERINUM ACIDI TANNICI, glycerite of Boroglycerin, 30 per cent boric acid in glycerin.
SUPPOSITORIUM ACIDI TANNICI, each suppository contains 3 gr. of boric acid.
TROCHISCUS ACIDI TANNICI, each lozenge contains ½ gr. tannic acid.
UNGUENTUM ACIDI TANNICI, 20 per cent tannic acid.
CATECHU, Gambir, 0.3 to 1 gram.
TINCTURA CATECHU, 2 to 4 mil.
KRAMERIA, 0.6 to 2 grams.
EXTRACTUM KRAMERIÆ SICCUM, 0.3 to 1 gram.
TROCHISCUS KRAMERIÆ, each lozenge contains 1 gr. of Krameria extract.
TROCHISCUS KRAMERIÆ ET COCAINÆ, each lozenge contains 1 gr. of extract of Krameria and $\frac{1}{20}$ gr. of cocaine hydrochloride.
TINCTURA KRAMERIÆ, 2 to 4 mil.
PASTA ACIDI TANNICI, paste of tannic acid, tannic acid jelly.
UNGUENTUM HAMAMELIDIS, ointment of hamamelis.

Other astringent drugs of this series, which offer no advantages over those already given are: Witchhazel (HAMAMELIS), the leaves and bark of Hamamelis Virginiana; Logwood (HÆMATOXYLON), the wood of Hæmatoxylon campechianum; Eucalyptus gum (KINO EUCALYPTI), obtained from several species of Eucalyptus; Nut-gall (GALLA), an excrescence on one of the oaks caused by the punctures and ova of an insect, Cynips Gallæ tinctoria. These are still contained in some pharmacopeias, but promise to follow a large number of similar bodies which have been discarded.

1. Charcoal

Charcoal is an efficient adsorbent of gases as well as of a variety of substances present in solution.

Kaolin, which also possesses adsorptive powers, has been advocated for uses similar to charcoal, particularly in diarrheal disorders.

Charcoal is used internally to remove the gases in flatulence and dyspepsia, and is prescribed in powder or in the form of charcoal lozenges. It may be given in any quantity, but is most commonly prescribed in 4 to 8 gram (60 to 120 gr.) doses. It has been advocated in poisoning with alkaloids and other vegetable poisons to take these up in the stomach and delay their absorption into the blood. It is employed externally as a deodorant in cases of foul ulcers, cancerous sores, or malodorous secretions from any source; for this purpose it is added to poultices or used dry in bags of fine cloth.

Carbo Activatus (U. S. P.), the residue from the destructive distillation of various organic materials, treated to increase its adsorptive power.

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VII. PURGATIVES

Purgatives are drugs which are employed in medicine to evacuate the bowel of its contents. Many drugs produce evacuation in the course of their action, but have other effects of importance and are not included in this class; for example the skin irritants if taken by the mouth may cause diarrhea, but this is accompanied by irritation of the mouth, throat and stomach, and these preclude their use as purgatives. The ideal purgative is devoid of any effects whatsoever, save in the intestine; it passes through the stomach without materially deranging its function, and is not absorbed, or at any rate has no significant action after absorption. The vegetable purgatives act through their irritant properties, which in some instances are elicited only by the action of the secretion of the intestines and of the neighboring glands. Thus some of the purgatives pass through the stomach in the form of bland, non-irritant compounds (castor oil), which are broken up by the digestive processes in the intestine, while others perhaps owe their activity in the intestine to their solution or suspension in the juices.

Many classifications of the purgatives have been based on their effects, and some of the terms are still retained, such as *aperient, eccoprotic, laxative, purgative, cholagogue, hydragogue, cathartic, or drastic.* But the effect of the purgatives is determined largely by the dose and by the condition of the intestine, so that a small dose may act as an aperient, laxative or eccoprotic, while a larger quantity of the same drug, or even the same dose in a more susceptible individual, may act as a drastic or hydragogue cathartic. They are therefore classified in three groups: (1) the mild aperients, castor oil group; (2) the purgatives of the anthracene series; (3) the jalap and colocynth group.

Symptoms.—In moderate doses the purgatives simply hasten the normal movements of the intestines, and the stool is of the ordinary appearance and consistency (laxative, aperient, or eccoprotic action). In larger quantities they cause a more profuse evacuation than normally, and the stools, which are repeated at short intervals, are of a looser, more fluid consistency. Their action may be accompanied by considerable pain and colic, and the hurried movements of the intestine are shown by the characteristic gurgling sounds. Large quantities of the more powerful purgatives may cause all the symptoms of acute enteritis, the stools at first contain the ordinary fecal substances accompanied by more fluid than usual, but later consist largely of blood-stained mucous fluid with little or no resemblance to ordinary feces. This violent purgation, which is not induced in therapeutics, is accompanied by pain and tenderness in the abdomen, and may induce shock, collapse, and eventually death.

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Action.—The peristaltic movements of the intestine which move the contents along the canal, arise from a complicated local reflex, which is aroused by the pressure of the contents on the sensory apparatus of the mucous membrane. This reflex may be increased (1) by anything that induces irritation of the mucous surface and thus renders it more sensitive to the pressure of the contents, and (2) by increasing the bulk of the contents until they exert more pressure on the mucous surface. The accelerated peristalsis after the vegetable and mercurial purgatives is due to their irritating the mucous membrane, while the purgation of the saline cathartics arises from their increasing the bulk and dilution of the contents. In neither case is there any reason to suppose that the neuro-muscular apparatus of the bowel is directly affected by the drugs; nor is the central nervous system implicated in the reflex whether normal or exaggerated by the purgatives.

In small quantities, such as are used in the vast majority of cases in therapeutics, the irritation produced by the vegetable purgatives is apparently only enough to accelerate peristalsis, and the fluid of the stools is drawn partly from the food and partly from the ordinary secretions of the digestive organs. In these cases the intestine is not actually inflamed, although some congestion may occur in it, as in all organs in a state of abnormal activity. On the other hand, when large quantities are ingested a true inflammation of the intestine occurs, manifested by increased movement, congestion, exudation of fluid into the lumen of the bowel, and pain. In these cases the intestine presents the usual signs of inflammation; it is red and congested, and contains a muco-purulent fluid and often blood. The origin of the fluid of the stools thus varies with the dose of purgative used; if it be small, the fluid is not an exudate, if it be large the fluid is partly an inflammatory product. The stools following the administration of purgatives differ from the normal feces in containing a larger proportion of water and also of soluble substances. In fact, they resemble rather the contents of the small intestine than the normal excreta, and contain bodies which would normally have been absorbed and utilized, but which have been hurried through the bowel too rapidly to permit of their being taken up by the epithelium.

The colic produced by purgatives is not due to the inflammation of the intestinal wall, but is explained by the more vigorous contractions of the walls of the bowel and the compression of the mucous membrane between the muscle and hard fecal masses in the large intestine. The tenderness produced by large quantities of the purgatives, on the other hand, would seem to indicate inflammation.

The different purgatives seem to act on different parts of the bowel (Magnus). Thus senna, and in all probability the other anthracene purgatives, appear to have no effect on the movements of the stomach and small intestine, but act only in the large intestine; the contents reach the colon at the normal rate, but as soon as they have left the small bowel, rapid movement begins and they are evacuated almost immediately. Castor oil on the other hand accelerates the peristalsis of the small intestine, through which the food passes very rapidly, while

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the large gut is much less irritated. Colocynth quickens the movement of both small and large intestine and considerable quantities of fluid are effused into the lumen. All three arrest the antiperistaltic movements in the large intestine.

Some of the purgatives cause evacuation of the bowel when they are injected subcutaneously or intravenously (senna, aloes, cascara, colocynth, podophyllum), and croton oil has long been rubbed on the skin in order to relieve constipation, and is found to cause intestinal inflammation and purging when injected intravenously. It has accordingly been suggested that these have a specific action on the bowel quite apart from their irritant effects; but it is probable that their intestinal effects are here due to their excretion into the bowel, which has been shown to occur in several instances. Other irritants applied subcutaneously or intravenously often produce similar effects on the alimentary canal.

The interval which elapses between the administration of a purgative and its effects varies with the dose, and also with the individual drug. In ordinary therapeutic doses, evacuation of the bowels occurs in most cases in five to ten hours, but if large quantities of the more powerful purges, such as jalap or croton oil, be given, the effects may be elicited in two hours. Aloes, cascara and podophyllum differ from the others in the length of the interval, catharsis rarely or never occurring earlier than ten to twelve hours after their administration, and often only after twenty to twenty-four hours.

The movement of the intestine induced by purgatives is accompanied by an increase in the leucocytes of the blood similar to that observed in other forms of intestinal activity, *e. g.*, during digestion.

The effects of the purgatives vary greatly in different animals. Thus, the rabbit is very refractory to most of the series, and often is killed by intestinal irritation without any evacuation being produced. The frog is unaffected by quantities which would produce poisoning in man, while the dog and cat respond much more readily.

It was formerly supposed that purgatives increased the secretion of bile, and certain of them, which were believed to have a special activity in this direction, were known as *Cholagogues*. It has been shown of recent years that none of them possesses any action on the secretion of bile, although they may increase its excretion by hurrying it through the intestine and preventing its reabsorption. On the other hand, the presence of bile in the intestine is a condition necessary to the activity of many of the purgatives. Thus Buchheim and Stadelmann found that in the absence of bile, podophyllum, jalap, scammony, rhubarb, and gamboge are either quite inactive or very much less powerful than usual. This is probably due to some solvent action of the bile, for Stadelmann found that when soaps were given with some of these drugs their activity returned, and in other cases a comparatively slight modification of their chemical form was sufficient to restore their activity, even in the absence of either bile or soap. Analogous results have been observed from causes other than the absence of bile; thus some of the pure principles of the purgatives are much less active than the crude drugs because the impurities of the latter alter their solubility. This alteration of the solubility may act in two ways: if the principle

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is rendered too soluble, it may be absorbed in the stomach and upper part of the bowel, and therefore fail to produce purgation; on the other hand, it may be rendered so insoluble that it fails to come into intimate contact with the bowel wall, and therefore does not irritate it. The effect of such colloid substances as the bile and gums is to delay the absorption of soluble substances in the upper part of the bowel and at the same time to keep the insoluble resins in suspension.

Few of the purgatives have any appreciable action after absorption, but general effects may be produced indirectly from their intestinal action. It is probable that reflexes are elicited by irritation of the bowel analogous to those discussed under skin irritants, but in addition, the congestion of the bowel produced by its activity must alter considerably the distribution of the blood in the body. The belief in the efficacy of a purge in congestion of the brain may thus be based on a true "revulsive" action; for the dilatation of the intestinal vessels may lower the blood-pressure and thereby lessen the blood supply to the brain. The congestion of the lower intestine is accompanied by a similar condition in the other pelvic organs, and those purgatives that act strongly on the large bowel, therefore often cause congestion of the uterus, with excessive menstrual flow, or, more rarely, in the case of pregnant women abortion. Lastly, a certain amount of fluid is withdrawn which would otherwise be excreted in the urine, which is found to be proportionately diminished in amount.

1. Mild Aperients, the Castor Oil Group

Castor Oil (Oleum Ricini) resembles olive oil in most respects, but on saponification forms ricinoleic acid instead of oleic acid. This acid ($C_{17}H_{32}(OH)COOH$) differs from the fatty acids obtained from ordinary oils in being unsaturated and in containing a hydroxyl group. Castor oil is itself a bland, non-irritating fluid, but on passing into the intestine is saponified by the pancreatic juice, and the ricinoleates thus formed are irritant and cause purgation. When the oil is saponified and the free acid given by the mouth, the effects are quite different from those of the oil, for the taste is acrid and unpleasant, and discomfort, nausea and vomiting may follow its ingestion from its irritant action on the stomach. The oil, on the other hand, has a bland, if unpleasant taste, and produces no effects on the stomach. Several other esters of ricinoleic acid have been shown by Meyer to resemble the glycerin ester (castor oil) in their purgative effects.

Castor oil is absorbed from the small intestine and thus does not act on the large intestine directly. In the tissues it disappears in the same way as an ordinary oil. It may be given in very large quantities without producing any symptoms, save those of a mild laxative, which induces evacuation in about six to ten hours. It is occasionally used as an emollient to the skin, and has been employed as a protective or emollient for application to the eye. The harmless nature of castor oil is shown by its use in China as an article of diet.

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In the beans from which castor oil is derived, a toxalbumin is found, which was at one time supposed to be the active principle of the oil. (See Ricin.) It has been shown, however, that the oil is entirely free from this poison, and that its action is due solely to the ricinoleate.

Castor oil is difficult to take owing to its unpleasant taste. It may be given alone, in an emulsion flavored with sugar and some volatile oil, in orange juice, spirits, or glycerin, or in flexible capsules.

Liquid Paraffin, a mixture of liquid hydrocarbons obtained from petroleum, is often used as a laxative, and, though its method of action is quite different from that of castor oil, it may conveniently be mentioned here. It has an oily consistency and is insoluble in water. It has practically no odor or taste. It is non-irritant, not acted on by the digestive ferments and is not absorbed. It acts mechanically partly by increasing the bulk of the intestinal contents and partly by softening the contents and acting as a lubricant. Liquid petrolatum is also available in the form of a flavored emulsion with agar.

It may pass through the intestinal canal without carrying with it the ordinary contents and in some patients it tends to escape from the anus in small quantities without causing an evacuation of the bowel. Occasionally it seems to retard digestion, probably from its coating food particles and preventing access of digestive ferments and its continued use may interfere with the absorption of the fat soluble vitamins (particularly vitamin A) and give rise to avitaminosis.

Sulfur (Sulfur, U. S. P.) is in itself an inert body but, while much the greater portion escapes in the stools unchanged when it is swallowed, some of it forms sulfides in the intestine, and these cause irritation, especially in the large bowel, increased peristalsis, and a soft, formed stool; in large quantities it has caused, in some instances, more severe symptoms with bloody evacuations. The sulfides form some hydrogen sulfide, which gives rise to eructation. Some 10 to 40 per cent of the sulfur taken by the mouth is absorbed as sulfide, which is excreted to a small extent by the lungs, giving the characteristic disagreeable odor to the breath, and to a much larger extent by the urine as sulfates and in organic combination. Sulfur may produce a slight diuretic and diaphoretic action.

Applied to the skin in ointment, sulfur appears to be changed in part to sulfide, particularly if some alkali be added; the sulfide is destructive to animal parasites and sulfur ointment has therefore been extensively used in the treatment of scabies. The ointment is rubbed into the skin after a hot bath and scrubbing with soap to open up the burrows of the insect. If applied too frequently it may produce irritation of the skin and a rash, but as a rule a few applications suffice to cure the disease. It may also be of value in skin disease through the sulfides tending to soften and dissolve the horny epidermis. For this purpose it may be associated with salicylic acid.

Glycerin.—When glycerin is injected into the rectum, it withdraws fluid from the mucous membrane and thus causes irritation, peristalsis, and evacuation of the bowels; the stool is of almost ordinary consistency, and no pain or colic is felt subsequently, nor does the remedy cause more than one evacuation. Glycerin may be injected into the

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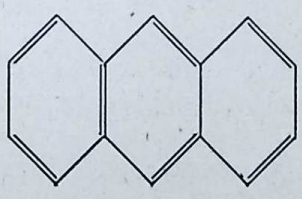
rectum for this purpose (dose 2–5 cc., ½–1 teaspoonful), but a more convenient form is the glycerin suppositories, **Suppositoria Glycerini**, which are made up with stearic acid and sodium carbonate, U. S. P., with gelatin, B. P. Glycerin suppositories are used in constipation instead of the ordinary aperients. Large doses of glycerin taken internally sometimes cause purgation, but it is not a reliable remedy when administered in this way. Instead of glycerin suppositories, small pieces of soap may be inserted in the rectum, and the same purpose may be served by the injection of a little strong soap solution in water.

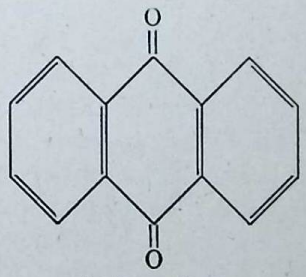
Glycerin in large quantities is poisonous, whether it is taken by the mouth or injected hypodermically or intravenously. It is true that no case of glycerin poisoning in man is known, but large doses are fatal to animals in the course of a few hours. The chief symptoms are restlessness, agitation, acceleration of the heart and respiration, general weakness, tremor and convulsions, which finally end in somnolence, coma, and death from failure of the respiration. Glomerulonephritis has also been observed in animals. Glycerin is absorbed rapidly from the intestine, and undergoes combustion in the tissues, only a very small fraction of it reappearing in the urine.

2. The Anthracene Purgatives and Phenolphthalein

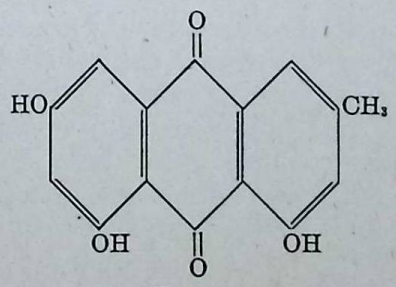
A number of purgatives, **Rhubarb, Senna, Aloes, Cascara** and **Frangula**, owe their activity to the presence of closely allied derivatives of anthraquinone which are known as emodins. The emodin of senna is trihydroxymethyl anthraquinone; that of rhubarb is dihydroxymethyl anthraquinone (*chrysophanic acid*); of aloes, tetrahydroxymethyl anthraquinone (*barbaloin*). Several active principles are usually present in each of the drugs and are combined to form glucosides. The composite mixtures of these active principles are sometimes designated as aloin (from aloes), frangulin (from frangula), etc.



Anthracene



Anthraquinone



Emodin

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None of the pure principles are as satisfactory in their action as the crude drugs, perhaps because they are less soluble in the intestine. For example, *aloin* is less certain in its effects than aloes, and crystalline aloin itself is inactive in the bowel, but is there changed under certain conditions to an amorphous compound which has irritant effects. The presence of bile in the intestine is not necessary to elicit the action of this group, except perhaps in the case of rhubarb.

The absorption of these bodies has not been satisfactorily determined in most cases. The urine is rendered yellow after rhubarb and senna, owing to the absorption and excretion of chrysophanol, but it is questionable whether the more active principles pass into the urine in appreciable amounts. When aloin is injected subcutaneously or intravenously, it is excreted for the main part into the bowel, and there produces irritation and catharsis. The yellow pigment of the urine after rhubarb and senna becomes a purple red on the addition of alkalies; the milk and skin also are said to assume a yellowish tinge from the presence of chrysophanol.

In the rabbit aloin seldom causes purgation, and is excreted by the kidney in considerable quantity, especially when injected hypodermically. In passing through this organ it causes marked irritation and epithelial necrosis, which often proves fatal in a few days. No irritation of the kidney occurs in man, the dog, or the cat after aloin. The anthracene purgatives have little action until they reach the large intestine, presumably because they do not find suitable conditions for solution in the small bowel. The interval between their administration and the evacuation of the bowel therefore tends to be longer than under most other purgatives; and for the same reason they tend to cause greater pelvic congestion. Among them aloes is especially slow in action and tends to cause congestion of the uterus.

Rhubarb contains a considerable amount of tannic acid, which acts as an astringent and therefore tends to cause constipation after the evacuation of the bowels. It is not well tolerated in some cases, its administration being followed by nausea, headache and giddiness, more rarely by skin eruptions of different kinds. Senna preparations are generally found to have a greater tendency to produce griping than the other members of this series.

Of these numerous preparations, the most extensively prescribed are the pills. The fluid preparations have an unpleasant, bitter taste, and are therefore less used, unless when disguised by the addition of sugar or volatile oils. The syrups of rhubarb and senna are often administered to children, and the confection of senna and the compound liquorice powder are also pleasant, easily taken preparations. The compound infusion or mixture of senna and the compound rhubarb powder are old and tried preparations, in which the virtues of the vegetable purgative are combined with those of a saline cathartic and antacid respectively; they are both possessed of a harsh, unpleasant taste. Cascara sagrada is a very popular remedy in habitual constipation, for which it is best given in small repeated doses, which can be gradually reduced as the condition of the bowel improves.

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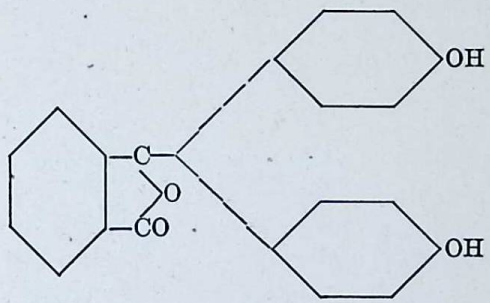
Phenolphthalein, long used by chemists as an indicator, is an effective cathartic and because of the ease with which it may be incorporated in confections is the active agent used in many proprietary preparations. It is very insoluble in water and is not irritant when applied to the ordinary mucous membranes. In the bowel it is dissolved by the bile and alkali and develops a mild irritant action in the small intestine and still more in the large intestine. Most of the phenolphthalein administered by the mouth is not absorbed but appears in the stools. A small amount undergoes absorption and is excreted by the kidney; if the urine is alkaline it is colored a brilliant pink. Phenolphthalein is practically not poisonous when injected intravenously in animals.



Phenolphthalein

It has a mild laxative effect when injected subcutaneously, and this arises from its being excreted into the bile and thus carried to the gut. In the large intestine it is reabsorbed into the blood and again carried to the liver and returned to the gut. It therefore acts for several days as a mild aperient, but as it is gradually eliminated in the urine and stools, the action passes off. The administration of phenolphthalein has led occasionally to the appearance of a peculiar eruption of the skin which in most cases consists of numerous polychromatic macular plaques of various sizes from a pin-head to several inches in diameter. The plaques may vary in color from a pink to a dark purple. The lesion is chronic and may last for months or even years, and when fading occurs a protracted pigmentation of the areas usually results. After the acute eruption has disappeared, relapses are common, especially if phenolphthalein be taken again, and the new lesions usually reappear on the site of the original eruption. The mucous membranes are also not infrequently involved.

Phenolphthalein is a white tasteless powder. It is administered in powder, pills, capsules or tablets in doses of 60 mg.

Several other dyes related chemically to phenolphthalein are used for diagnostic purposes. **Phenolsulfonphthalein** or phenol red is injected in the form of a solution of its sodium salt in doses of 6 mg. for determining the renal function. This dye is almost entirely excreted by the normal kidney and hence by determining the rate of its excretion an estimate is obtained of the functional capacity of the kidney.

Phenoltetrachlorophthalein (bromsulfalein) is excreted by the liver and is used in determining hepatic function. Its failure to be removed from the blood stream following its intravenous injection is evidence of hepatic dysfunction.

Phenoltetraiodophthalein (phentetiothalein) is also excreted by the liver and because of its iodine content is radiopaque. Hence it is used to visualize the

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gall bladder and determine its functional activity. It should not be used in patients with myocardial insufficiency, uremia or jaundice. Tetraiodophenolphthalein (iodophthalein) is also used for gall bladder visualization.

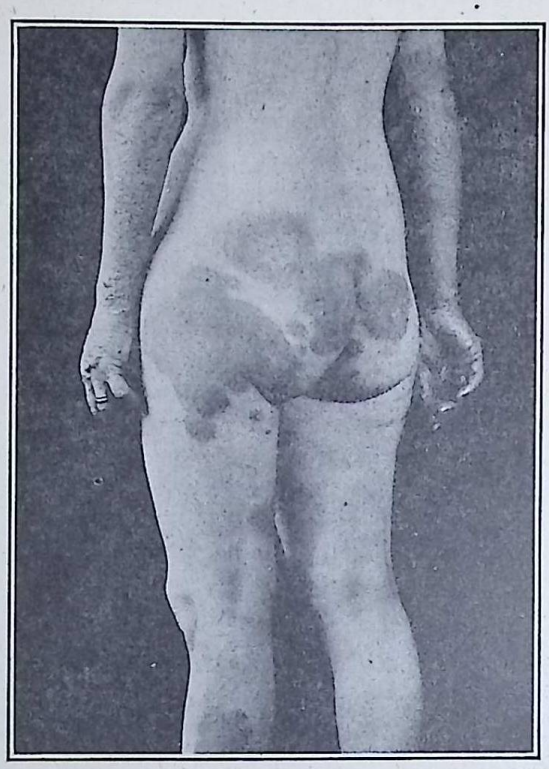

FIG. 10.—Typical phenolphthalein eruption. (Ormsby and Montgomery's Diseases of the Skin, Lea & Febiger.)

3. The Jalap and Colocynth Group

The third group of the vegetable purgatives comprises a number of resinous glucosides and acids, whose more intimate chemical structure is unknown, though a number of them appear to be nearly related chemically, so that it is possible that they all contain a common radicle like the members of the anthracene group.

Jalap resin contains two anhydride glucosides, *Convolvulin* and *Jalapin*, the latter only in very small quantity. Scammony consists very largely of *Jalapin*. Podophyllum contains two isomeric principles, *Podophyllotoxin* and *Picropodophyllin*. *Colocynthin* is a glucoside occurring in the colocynth fruit, and forms *Colocynthein* and sugar when treated with acids.

Action.—These substances are in general much more powerful than any of the other purgatives, and are therefore classed together as the drastic purgatives or hydragogue cathartics. In small quantities they cause evacuation more rapidly than the anthracene purgatives, and in somewhat larger doses produce profuse watery stools with much pain and often tenesmus. In cases of poisoning, the bowel undergoes acute inflammation, and blood is passed in the stools, which often contain shreds of epithelium from the walls. The irritant action ap-

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parently is not confined to the bowel, for their administration is sometimes followed by uneasiness in the stomach, and occasionally by nausea and vomiting. On the other hand, moderate quantities are said not to induce colic so frequently as some of the anthracene purges. This is probably due to the fact that they accelerate the movement of both the small and large bowel; a quantity of unabsorbed fluid is thus poured into the cecum and the contents are rendered softer and more easily moved than if these drugs, like the anthracene group, acted only on the large intestine. In the cat, jalap resin quickens the peristaltic movements of the small intestine, while on the colon it has rather a constipating effect, possibly due to an increase of the antiperistaltic movements of the proximal colon (Bloch).

Several of these resinous purges are irritant to the skin and especially to the mucous membranes of the eye, nose, and throat. The presence of bile in the intestine increases the purgative action of almost all these bodies, and in fact, seems essential for the action of most of them.

Podophyllotoxin and colocynthin cause purgation when injected subcutaneously; this is probably owing to their excretion into the bowel, as the former has been detected in the feces after this method of administration. Podophyllotoxin causes glomerular nephritis and hemorrhages into various organs when administered hypodermically or intravenously in large quantities, and when added to blood in a test-tube, it causes the formation of methemoglobin in the corpuscles. It has been said to have a depressant action on the central nervous system, but this is probably a result of the shock and hemorrhage produced by its intestinal action. Colocynthin is said to cause renal inflammation when applied subcutaneously or taken internally, and even when the powder is inhaled during its manufacture. Jalapin and convolvulin given by the mouth are found in the feces in a partially decomposed state; none appears in the urine.

The resinous purgatives are generally administered in pill form; very frequently two or more are combined in one pill, or they may be prescribed along with extract of belladonna or hyoscyamus, or with a drop of some carminative oil to prevent the pain and griping which often accompanies their action. The importance of these purgatives is much less than it was formerly, and they are seldom used in modern therapeutics. Podophyllum is used for local application to the lesions of **Granuloma Inguinale** and to **Condylomata.**

Therapeutic Uses of the Purgatives.—The purgatives are employed to cause evacuation of the bowel when for any reason its peristalsis is slow. With a host of effective medicinals at his disposal, the modern physician is less concerned with prescribing cathartics than was his predecessor of a previous generation. The general laity, on the other hand, indulges freely in self medication with various forms of proprietary cathartic preparations. Mineral oil, cascara, saline cathartics, and proprietary preparations containing phenolphthalein are the popular home remedies. In the choice of a purgative, the advantages of the vegetable purgatives must be weighed against those of the saline cathartics and of the mercurial preparations. In ordinary *constipation of short standing*, in which the peristalsis may merely seem somewhat more sluggish than usual, the milder laxatives are prescribed—castor oil, sulfur, senna, rhubarb, aloes, frangula, or cascara sagrada. The first two cause least disturbance of the bowel, but are disagreeable to take, and are less commonly pre-

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scribed for adults than rhubarb or cascara, or small doses of colocynth or podophyllum. In children or in debility in adults, senna and castor oil are frequently used; sulfur is often given along with magnesia in constipation in children, and in hemorrhoids, because it renders the stools softer and less liable to cause irritation mechanically.

In *chronic constipation* which cannot be controlled by hygienic measures, or by the use of a special dietary such as fruits or coarse foods, and where the intestine has apparently taken on a sluggish habit, cascara, rhubarb, aloes, phenolphthalein, or colocynth may be ordered, but the saline cathartics often prove more satisfactory. Rhubarb tends to cause some constipation after its laxative effects, but is often used in these cases, as it possesses some bitter stomachic action, which compensates for its astringent after-effects. In obstinate constipation, in which the bowel contains hard fecal masses, the milder purgatives often provoke griping without relieving the condition, and in these cases larger doses of colocynth, jalap, podophyllum, or croton oil are sometimes used, along with some of the extracts of the atropine group or with a carminative oil. They may be prescribed along with some of the saline cathartics, as in the compound infusion of senna or the compound powder of jalap. An enema may with advantage be given previously.

In some forms of *diarrhea* constant irritation seems to be kept up by the presence of irritants in the bowel, and the indications are the removal of these by a purge rather than the administration of astringents. Castor oil is especially adapted for this purpose.

The more powerful purgatives were formerly largely used to remove fluid from the body in cases of *dropsy* or edema, but the more effective diuretics have displaced them for this purpose.

The purges act as *intestinal disinfectants* by removing the microorganisms mechanically, though the vegetable purges are less used for this purpose than calomel or salines. A purgative is administered to remove poisons in the intestine when they have passed beyond the stomach or when they are excreted into the bowel.

Special mention must be made of *postoperative atony* of the intestine. In this condition the most effective remedies are neostigmin, posterior pituitary extract, or the application of hot packs (turpentine stupes) to the abdomen.

Purgatives are *contraindicated* in conditions of acute intestinal irritation and intestinal obstruction. These should be given with care during menstruation and pregnancy, owing to the congestion of the pelvic organs, which may lead to an excessive flow in the one case and to abortion in the other; aloes is especially dangerous in these conditions. In collapse, asthenia and anemia, powerful purgatives are contraindicated, owing to the irritation they produce. In hemorrhoids, aloes is often said to do harm by increasing the congestion of the rectum, and powerful purges are injurious from the straining they cause, but if constipation is present, a mild purgative is beneficial. The promiscuous use of cathartics by the laity for abdominal pain has led to dire results in cases of appendicitis.

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4. Saline Cathartics.

Dilute solutions of such salts as the chlorides, iodides, and bromides of the alkalies are absorbed rapidly from the alimentary canal, but some of the other salts of these metals apparently permeate the epithelium with greater difficulty, and their solutions therefore remain unabsorbed for a longer time in the intestine. The contents of the intestine and the stools thus contain more fluid than usual and these salts are known as the saline cathartics. The chief salts of sodium and potassium which have this intestinal action are the sulfates, phosphates, tartrates and citrates; less known ones are the malates and ferrocyanides.

In these effects the acid constituent, or anion, is obviously the chief factor, for the same base, or cation, is present in readily absorbed salts such as the chlorides. And no pronounced differences between the action of chlorides and sulfates are observed, unless the salt can be given in large quantities, as is possible in the case of the salts of the alkalies. The effects of the sulfate and hydrochloride of morphine, for example, may be taken as identical, because the anion is present in so small amount as to be practically inert.

The cation of a salt may also fail to be taken up readily by the bowel; for example, magnesium chloride is absorbed slowly although other chlorides permeate rapidly, and magnesium salts thus act as purgatives in the same way as sulfates. When both ions are slowly absorbed as in the case of magnesium sulfate, the cathartic action is naturally more powerful than when only one has this character.

The chief saline cathartics used in therapeutics are the *sulfate of sodium* (Glauber's salt), the *sulfate of magnesium* (Epsom salt), the *double tartrate of sodium and potassium* (Rochelle salt) and the *phosphate of sodium*. In addition the *oxide* and *carbonate of magnesium* have some purgative action from being formed into soluble salts in the stomach and intestine.

Symptoms.—Most of the cathartics have a harsh, bitter, unpleasant taste, and when taken in concentrated solution, may induce some nausea, partly from the taste, and partly from the "salt-action" on the stomach, which they possess like other soluble bodies. Dilute solutions, however, provoke no such symptoms, but after one or two hours induce a profuse watery evacuation of the bowels. This is sometimes preceded by some pain and griping, but these are not nearly so frequent or so severe as after the vegetable purgatives. Not infrequently the urine is increased in amount afterward, or it may be found to have an unusually high percentage of salts. If a moderate quantity of a dilute solution be given, only one evacuation follows, but large doses of concentrated solutions induce repeated stools, which at first contain some fecal matter, but later consist mainly of bile-stained mucous fluid.

Action: Intestine.—The saline cathartics differ from the vegetable purgatives in not inducing irritation of the intestine, unless when they are given in very large quantities. The characteristic effect is not irritation, but retarded absorption. The slow absorption of the salt entails the slow absorption of the fluid in which it is dissolved, for the

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salt holds on to the water and only permits of its being taken up by the bowel if an equivalent amount of salt is also absorbed. If a solution of sodium chloride isotonic with the blood serum be administered by the mouth to a dog with a cecal fistula, little or none of it reaches the wound, as it is all absorbed in the stomach and small intestine. If, on the other hand, an equal amount of an isotonic solution of sodium sulfate be administered in the same way, most of the solution escapes by the fistula, only some 10 to 20 per cent having been absorbed by the stomach and small intestine. In a normal dog or in the human subject, a much larger amount of fluid therefore reaches the large intestine if sodium sulfate be dissolved in it than if sodium chloride be used instead. The contents of the large intestine are consequently more fluid than usual, and are passed down more easily toward the rectum. At the same time the weight and distention of the bowel induces increased peristalsis and the whole is evacuated. This increased peristalsis is due, however, not to any irritant action such as has been found to be induced by rhubarb or croton oil, but to the large amount of fluid contents, which arouses the usual peristaltic reflex.

This accelerated passage along the bowel has been observed in man by means of the roentgen-rays, and appears to resemble that previously described in animals. When the distended small intestine empties its contents into the colon, the large bowel adopts a more rapid but otherwise normal movement and this leads to the evacuation of the rectum; the first stool may thus be of almost normal consistency, but this is generally followed by a profuse watery movement which may contain the greater part of the salt administered.

If a weaker solution of sodium sulfate is administered, the only difference is that more of the fluid is absorbed and less reaches the large intestine; but however weak the solution, more of it reaches the large intestine than if a correspondingly weak solution of common salt had been given. An isotonic or hypotonic solution of a saline cathartic may produce purgation more rapidly than a more concentrated solution for the latter may cause contraction of the pyloric sphincter, so delaying the escape of the salt into the intestine.

If a hypertonic solution be administered, the effect is somewhat different. The salt is still unabsorbed, but it draws fluid from the blood into the bowel from its having higher osmotic pressure than the blood. A similar draining of the body fluids occurs when concentrated solutions of common salt reach the bowel, but the cathartic salts are much more powerful, because they do not pass out of the bowel into the blood so easily. Instead of an exchange of salt and fluid being carried on between the blood and intestinal contents, the blood gives up its fluid without any sufficient compensation in salt. Eventually the intestinal fluid becomes isotonic, and then some absorption of both salt and fluid occurs; in fact, some salt has been absorbed all along, as the epithelium is not absolutely impermeable to the cathartics. But much less of the sulfate is absorbed than of the chloride given in equal concentration, and as a general rule a strong solution causes such an accumulation of fluid that the bowel becomes distended and evacu-

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ates its contents. If, however, from any cause this fails to occur, a gradual absorption follows and the whole salt and fluid in the bowel is absorbed. These salts may fail to purge, for example, when the blood and tissues contain very little fluid, as in animals which have been deprived of water for several days previously. In this case the osmotic pressure in the bowel is unable to draw fluid from the concentrated blood, which on the other hand has a higher attraction for the fluid in the bowel than usual. But where large quantities of fluid are present in the tissues, as in edema and dropsy, the saline cathartics drain them through the blood into the bowel, and very profuse evacuation occurs, with the disappearance of the exudate.

The saline cathartics induce certain changes in the **Blood** indirectly through their action on the intestine. They prevent the absorption of the fluid of the food, or, if in sufficient concentration, actually draw fluid from the blood and tissues into the bowel, and under both conditions the blood becomes more concentrated than usual; in the first case because it is not reinforced by the usual amount of fluid from the food, in the second because it actually loses fluid into the intestine. This concentration of the blood leads to a sensation of thirst, and to a lessened excretion of fluid by the kidneys and other glands.

A certain amount of salt and of fluid is absorbed from the intestine, unless purgation follows very rapidly, and this salt acts in the blood and tissues in the same way as the salts which do not act as cathartics. When very dilute solutions of these salts are given, therefore, the blood becomes less concentrated and diuresis follows, but this does not occur so soon as after a similar solution of common salt, because the absorption is somewhat slower. Stronger cathartic solutions at first cause a concentration of the blood and lessened urine, but afterward the excess of salt in the blood may cause diuresis. The greater the purgative action, the less the diuretic, because more fluid and more of the cathartics are thrown out in the stools. If no purgation follows for any reason, as when the blood has been concentrated by long abstinence from water, the whole of the salt eventually passes into the blood and is excreted by the kidney, and may cause very considerable diuresis and a still further concentration of the blood. The sulfates are absorbed by the epithelium of the renal tubules with much greater difficulty than chloride, and thus offer osmotic resistance to the absorption of the fluid in the tubules; sulfates absorbed into the blood therefore induce a more profuse diuresis than an equal amount of chloride, but less of the former reaches the blood generally, so that the chlorides are better practical diuretics.

From the above it can be inferred at once that a saline cathartic injected intravenously causes no purgation, for instead of preventing the passage of fluid from the bowel into the blood, it rather encourages its absorption by increasing the osmotic pressure of the blood. And similarly the hypodermic injection of these salts is not followed by purging.

The statement is sometimes made that the saline cathartics act as

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cholagogues, *i. e.*, increase the secretion of bile, but this has not been confirmed by more careful observations.

The **Temperature** is often somewhat reduced by the action of the saline cathartics, but seldom more than one-half degree.

The habitual use of saline cathartics has been advocated for **Reducing the Weight** in obesity, but any effect which they induce can only result from a reduced absorption of nutrients from the bowel. Obviously, the limitation of the caloric intake is a more effective and rational procedure for reducing the weight.

When purgation follows the administration of a saline cathartic, the most of the salt escapes in the feces, never having been absorbed at all. When the salt fails to purge, however, and is absorbed, it undergoes the usual exchanges in the tissues and is excreted by the urine.

The **Sulfates** seem to pass through the tissues without injuring them, and but little effect is observed from injecting considerable quantities into the blood. When the sulfate ion is combined with a poisonous base, such as potassium or magnesium, the injection is of course followed by characteristic symptoms; but the anion seems to be comparatively harmless, and when the potassium or magnesium salt is taken by the mouth it also is quite devoid of general action. However, in nephritis where renal insufficiency interferes with their excretion, accumulation of these ions to toxic levels may ensue.

The **Phosphates** are also very inactive after absorption. When they are injected subcutaneously or intravenously, the metaphosphates and pyrophosphates are poisonous. Phosphates absorbed in man and in the carnivora are excreted by the kidney and increase the acidity of the urine; in the herbivora they are excreted exclusively by the bowel wall.

The **Tartrates** are slowly oxidized in the tissues to carbonates but a considerable quantity is excreted in the urine unchanged. Injected into the blood directly, the tartrates seem to act as heart poisons, and in the rabbit nephritis is induced by their hypodermic application, but no such effects are observed in man from their administration by the mouth even in enormous quantities.

The oxide and carbonate of magnesium differ from the other saline cathartics in being very insoluble and in possessing an alkaline reaction. Part of that ingested is formed into magnesium chloride in the stomach, however, and the carbonic acid present in the intestine may dissolve part by forming the bicarbonate. Their alkalinity serves to remedy any excessive acidity of the stomach or intestine, while at the same time they are mildly cathartic. The prolonged use of large quantities of magnesia has in some cases led to the formation of large concretions in the bowel, resulting in obstruction.

Therapeutic Uses.—The saline cathartics are very largely used to relieve constipation. Habitual constipation seems to be caused by insufficient peristalsis, and the slow passage of the contents through the intestines allows of a more complete absorption than usual, this in turn rendering the feces hard and dry and difficult to move onward. The saline cathartics increase the fluidity of the intestinal contents, and thus facilitate their expulsion, and this is probably the only effect they have when taken in small quantities, and especially in dilute solution as in the natural mineral waters. In larger quantities, however, more water is retained in the bowel, and the weight and distention cause peristalsis, while in sufficient quantity they draw fluid

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from the blood and cause profuse watery discharges. When a very complete evacuation is desired, the saline cathartics may be given along with some of the vegetable purgatives. Such mixtures are the official Black Draught (see Senna) and the compound powder of Jalap. The saline cathartics act much more rapidly than the vegetable purgatives, and a common method of combining their effects is to give the latter in the evening and the saline the following morning; in the same way a mercurial purge, such as calomel, given in the evening, may be followed by a Seidlitz powder in the morning.

The chronic constipation due to sedentary habits is much benefited by the saline cathartics, more especially by dilute solutions taken before breakfast. The sulfates and tartrates are harsh and unpleasant to the taste, and the natural waters are often preferred, or one of the effervescent preparations may be used in those cases.

The sulfates and tartrates are more frequently used where a single large dose has to be prescribed in order to empty the bowel, but there also the Seidlitz powder may be advised instead, as being more agreeable to the taste. The saline cathartics are less liable to cause pain and griping than vegetable purgatives, and thus tend to disturb the patient less.

Sodium phosphate may be prescribed for children, either as a powder to be given in jelly, or in solution in milk or other food which completely hides its taste.

The saline cathartics are used to lessen intestinal putrefaction, and are sometimes very efficient, though they do not act through any antiseptic power, but simply by removing the putrefying mass. The phosphate of sodium has been especially recommended in some forms of diarrhea in children. It is also commonly used in adults to relieve flatulence and vague abdominal discomfort.

The saline cathartics were formerly often administered to remove accumulations of fluid in the body arising from cardiac or renal insufficiency, or from an old effusion. For this purpose the sulfate of magnesium was used in a large dose, dissolved in about its own weight of water. This form of treatment is liable to weaken and depress the patient, and is specially contraindicated, therefore, in asthenic conditions. More effective methods of removing accumulations of fluid by the use of diuretics and cardiac remedies (see Digitalis) are now utilized.

An analogous effect may play a rôle in reducing intracerebral pressure. Cushing found that hypertonic sodium chloride solution given by the mouth relieved high pressure of the cerebrospinal fluid, presumably by withdrawing the fluid of the blood by diuresis; the injection into the rectum of 6 to 8 oz. (200 cc.) of a 25 per cent solution of magnesium sulfate is used for the same purpose, acting by withdrawing fluid from the blood into the intestine.

Magnesia and magnesium carbonate are less liable to purge than the soluble salts, and are specially indicated in hyperacidity of the stomach or in acid putrefaction in the bowel. They cause less disturbance of the digestion than the carbonates of the alkalies because of their insolubility, and at the same time have the advantage of acting as mild

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purgatives, while the insoluble alkaline lime preparations, tend to induce constipation. The magnesia preparations may be used also in diarrhea as antacids, as they have no irritant action on the bowel. A combination of antacid, carminative, saline and vegetable aperient is found in Gregory's powder, which contains magnesia, rhubarb, and ginger. Freshly prepared magnesia is recommended in arsenic poisoning to form an insoluble precipitate in the stomach, and in poisoning with acids it is also of value when it can be obtained readily. In both cases it is to be given in large quantities.

The phosphates, hypophosphites and glycerophosphates were formerly prescribed as tonics in the mistaken belief that they improved nutrition and aided in the metabolic activity of the nervous system. There is no basis for their use for these purposes.

Natural mineral waters have also been used instead of the pharmacopeal preparations. These contain the sulfates of sodium and magnesium with small amounts of other salts. The belief in their mystical virtues is a survival of the old superstitious faith in the healing properties of springs.

Agar and Psyllium Seeds

Although having no chemical relation to the saline cathartics, several laxatives may be mentioned here which act in an analogous manner. Agar and various products derived from psyllium seeds absorb water from the gut thus increasing the fecal mass and stimulating peristalsis.

Agar is the dried extract of various species of seaweed (Gelidiaceæ) and consists mainly of gelose, a carbohydrate which is indigestible and unabsorbable and retains water in the alimentary canal in the same way as the saline cathartics. It thus increases the bulk of the contents of the bowel and causes their evacuation in constipation. Agar is a tasteless grayish white powder which is administered by suspension in water or in food in chronic constipation in doses of 10 grams.

Psyllium, plantain or plantago seed contains a mucilage which is indigestible and like agar swells in the gut and is used as a mild laxative. When fed to animals, ground plantago seeds induce darkening of the kidneys and the deposition of microscopic pigment in the tubules. The significance of this is unknown. Psyllium seed is administered with water or fruit juices, eaten without mastication, or mixed with hot water and the resulting gelatinous mass spread on bread. It is used in doses of 4 to 15 grams. Metamucil is a mixture prepared from psyllium seeds to which sugar and salts in small amount are added.

Preparations

Aperients

Agar (U. S. P., B. P.), agar-agar, a dried mucilaginous substance extracted from *Gelidium* and closely related algæ. Dose, U. S. P., 4 grams; B. P., 4 to 16 grams.

Confecum Sulphuris (B. P.), confection of sulfur. Dose, 4 to 8 grams.

Emulsum Petrolati Liquidi (U. S. P.), mineral oil emulsion, containing acacia, syrup, vanillin and alcohol. Dose, 30 cc.

Oleum Ricini (U. S. P., B. P.), a fixed oil expressed from the seed of *Ricinus communis*. Dose, U. S. P., 15 cc.; B. P., 4 to 16 mil.

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PETROLATUM LIQUIDUM (U. S. P.), PARAFFINUM LIQUIDUM (B. P.), white mineral oil. Dose, U. S. P., 15 cc.; B. P., 7.5 to 30 mil.

PETROLATUM LIQUIDUM LEVE (U. S. P.).

SULFUR PRÆCIPITATUM (U. S. P.), precipitated sulfur.

SULFUR SUBLIMATUM (U. S. P.), sublimed or flowers of sulfur.

SUPPOSITORIA GLYCERINI (U. S. P., B. P.), glycerin suppositories.

Rhubarb

EXTRACTUM RHEI (U. S. P.). Dose, 0.5 gram.

PILULA RHEI COMPOSITA (B. P.), contains rhubarb, aloes, myrrh, and oil of peppermint. Dose, 0.25 to 0.5 gram.

PULVIS RHEI COMPOSITUS (B. P.), Gregory's Powder, contains rhubarb, light and heavy magnesia and ginger. Dose, 0.6 to 4 grams.

RHEUM, rhubarb, the rhizome of Rheum officinale and other species. Dose, U. S. P., 1 gram; B. P., 0.2 to 1 gram.

SYRUPUS RHEI AROMATICUS (U. S. P.). Dose, 10 cc.

TINCTURA RHEI AROMATICA (U. S. P.), contains several volatile oils. Dose, 4 cc.

TINCTURA RHEI COMPOSITA (B. P.), formed from rhubarb, cardamom and coriander. Dose, 2 to 4 mil.

Senna

CONFECTIO SENNÆ (B. P.). Dose, 4 to 8 grams.

FLUIDEXTRACTUM SENNÆ (U. S. P.). Dose, 2 cc.

EXTRACTUM SENNÆ LIQUIDUM (B. P.). Dose, 0.6 to 2 mil.

INFUSUM SENNÆ CONCENTRATUM (B. P.). Dose, 2 to 4 mil.

INFUSUM SENNÆ RECENS (B. P.). Dose, 15 to 60 mil.

MISTURA SENNÆ COMPOSITA (B. P.), Black Draught, formed from magnesium or sodium sulfate, liquorice, compound tincture of cardamom, aromatic spirits of ammonia, and infusion of senna. Dose, 30 to 60 mil.

SENNA (U. S. P., B. P.), the leaflets of Cassia acutifolia (Alexandrian senna), and of Cassia angustifolia (Indian senna). Dose, 4 grams.

SENNÆ FRUCTUS (B. P.), Senna Pod, the dried ripe fruit of Cassia acutifolia or angustifolia.

SYRUPUS SENNÆ (U. S. P., B. P.). Dose, U. S. P., 8 cc.; B. P., 2 to 8 mil.

Aloes

ALOE (U. S. P., B. P.), the inspissated juice of the leaves of several species of aloe.

ALOINUM (U. S. P.), a mixture of the active principles obtained from aloes. Dose, 15 mg.

PILULA ALOES (B. P.). Dose, 0.25 to 0.5 gram.

PILULA ALOES ET ASAFŒTIDÆ (B. P.) Dose, 0.25 to 0.5 gram.

PILULA ALOES ET FERRI (B. P.). Dose, 0.25 to 0.5 gram.

Cascara

CASCARA SAGRADA (U. S. P., B. P.), the bark of Rhamnus Purshiana.

ELIXIR CASCARÆ SAGRADÆ (B. P.). Dose, 2 to 4 mil.

EXTRACTUM CASCARÆ SAGRADÆ (U. S. P.). Dose, 0.25 gram.

EXTRACTUM CASCARÆ SAGRADÆ LIQUIDUM (B. P.). Dose, 2 to 4 mil.

EXTRACTUM CASCARÆ SAGRADÆ SICCUM (B. P.). Dose, 0.1 to 0.5 gram.

FLUIDEXTRACTUM CASCARÆ SAGRADÆ (U. S. P.). Dose, 1 cc. (15 min.).

FLUIDEXTRACTUM CASCARÆ SAGRADÆ AROMATICUM (U. S. P.). Dose, 2 cc. (30 min.).

Phenolphthalein

PHENOLPHTHALEINUM (U. S. P., B. P.), a crystalline white or faintly yellowish powder. Dose, U. S. P., 60 mg.; B. P., 0.06 to 0.3 gram.

TABELLÆ PHENOLPHTHALEINI (B. P.), tablets of phenolphthalein. Dose, 0.06 to 0.3 gram.

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Drastics

COLOCYNTHIS (B. P.), colocynth, the pulp of the fruit of Citrullus colocynthis deprived of its rind.

EXTRACTUM COLOCYNTHIDIS COMPOSITUM (B. P.) (containing colocynth, aloes, scammony and cardamom). Dose, 0.25 gram.

IPOMŒA (B. P.), the dried root of Ipomœa orizabenzis, Mexican scammony root, Orizaba jalap root. Dose, 0.3 to 1.2 grams.

JALAPA (B. P.), the tuberous root of Ipomœa Purga. Dose, 0.3 to 1 gram.

PILULA COLOCYNTHIDIS ET HYOSCYAMI (B. P.) (colocynth, aloes, scammony, resin, oil of cloves, and extract of hyoscyamus). Dose, 0.25 to 0.5 gram.

PODOPHYLLUM, the rhizome and roots of Podophyllum peltatum, the May apple.

RESINA PODOPHYLLI (B. P.). Dose, 0.01 gram; B. P., 0.015 to 0.06 gram.

SCAMMONIÆ RESINA (B. P.), a mixture of resins obtained from Ipomœa. Dose, 0.03 to 0.2 gram.

Saline Cathartics

MAGMA MAGNESIÆ (U. S. P.), contains about 7 per cent of Magnesium Hydroxide. Dose, antacid, 4 cc.; laxative, 15 cc.

MAGNESII CARBONAS, a mixture of carbonate and hydrate of magnesium. Dose, U. S. P., as antacid, 0.6 gram, as laxative, 8 grams; B. P., 0.6 to 4 grams.

MAGNESII OXIDUM, magnesia (MgO) (U. S. P.). Dose, as antacid, 0.25 gram, as laxative, 3 grams; B. P., dose, 0.6 to 4 grams.

MAGNESII SULFAS (U. S. P.), MAGNESII SULPHAS (B. P.), Epsom salts ($MgSO_4$, $7H_2O$), soluble in $1\frac{1}{2}$ parts of cold water. Dose, U. S. P., 15 grams; B. P., 2 to 16 grams.

MISTURA MAGNESII HYDROXIDI (B. P.), contains about 8 per cent of hydroxide. Dose, 4 to 16 mil.

POTASSII BITARTRAS (U. S. P.), POTASSII TARTRAS ACIDUS (B. P.), cream of tartar ($KHC_4H_4O_6$), a crystalline powder with a pleasant acidulous taste. Dose, U. S. P., 2 grams; B. P., 1 to 4 grams.

POTASSII ET SODII TARTRAS (U. S. P.), SODII ET POTASSII TARTRAS (B. P.), Rochelle salt ($KNaC_4H_4O_6 \cdot 4H_2O$), crystals or powder with a cool saline taste. Dose, U. S. P., 10 grams; B. P., 8 to 16 grams.

POTASSII SULPHAS (B. P.), potassium sulphate, K_2SO_4. Dose, 1 to 3 grams.

SODII PHOSPHAS (U. S. P., B. P.) ($Na_2HPO_4 \cdot 12H_2O$), a crystalline salt with a cool, saline taste, soluble in about 6 parts of cold water. Dose, 4 grams.

SODII SULFAS (U. S. P.), SODII SULPHAS (B. P.), Glauber's salt (Na_2SO_4,-$10H_2O$), soluble in about 3 parts of cold water. Dose, U. S. P., 15 grams; B. P., 2 to 16 grams.

SODII SULPHAS EXSICCATUS (B. P.), exsiccated sodium sulfate, anhydrous sodium sulfate, exsiccated Glauber's salt, Na_2SO_4. Dose, 1 to 8 grams.

Effervescing Preparations

LIQUOR MAGNESII CITRATIS (U. S. P.) is a solution of magnesium citrate with excess of citric acid to which potassium bicarbonate is added. The whole is bottled tightly and effervesces when the cork is removed. Dose, 200 cc.

PULVIS EFFERVESCENS COMPOSITUS (U. S. P., B. P.), Seidlitz powder. This powder is made up in two papers, of which the blue one contains a mixture of 3 parts of Rochelle salts and 1 part of sodium bicarbonate, in all 10 grams, while the white paper contains 2.2 grams of tartaric acid. When the powders are dissolved separately in water and the solutions mixed, the tartaric acid acting on the bicarbonate releases carbonic acid with effervescence.

SODII PHOSPHAS EFFERVESCENS (B. P., U. S. P.). Dose, 10 grams.

SODII SULPHAS EFFERVESCENS (B. P.), a mixture containing the sulfate of soda instead of citrate of magnesia. Dose, 4 to 16 grams.

Many other effervescent mixtures are used instead of the official ones —among them the tartrates and citrates of the alkalies, the acetate of magnesium, etc. The effervescent preparations are always to be taken

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in solution in about a tumbler of water; in some instances in which this was not understood, severe distention of the stomach with alarming symptoms have arisen from the carbonic acid being freed in the stomach. The effervescent preparation ought to be kept dry, and the solution of magnesium citrate has to be kept tightly corked.

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PART III.

Substances Characterized Chiefly By Their Action After Absorption

A. DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM

I. NARCOTICS OF THE METHANE SERIES

1. Alcohol-Chloroform Group

A LARGE number of the simpler methane compounds of the open-chain series cause depression of the central nervous system, more especially of the cerebrum, and some of them are perhaps the most extensively used of all drugs for among them are the universally used surgical anesthetics, alcohol and the hypnotics. The General action of all of these is similar in character and consists of a first stage of imperfect consciousness and confused ideas and analgesia, followed by a second stage of excitement or delirium and a third stage of complete unconsciousness or surgical anesthesia. A non-therapeutic fourth stage of medullary paralysis usually due to overdosage can occur. The second stage is much more marked after ether and chloroform since with other drugs of this series, it is often entirely absent. This has given rise to the theory that these drugs stimulate the nerve cells before paralyzing them, but an alternative explanation is that the functions of control and inhibition are lessened and the centers of motion are thus left free and act more strongly than normally. Current thought strongly favors the inhibition concept. This question will receive greater attention under the discussion of alcohol.

The action on the central nervous system of most mammals is of greatest importance and is elicited by comparatively small quantities of these drugs, but other forms of living matter are also affected by them in somewhat greater concentration, and their action here may in short be considered as coëxtensive with life.

The different members of the group vary greatly in their chemical affinities, and no definite relation can be found between their narcotic action and the presence of any one radical. This suggests that their effects depend on the properties of the molecule as a whole, and not on a chemical combination being formed with any constituent of the tissues. The most widely accepted theory has been suggested by Meyer and Overton, who attribute the common action of these narcotics to a common physical character. They point out that practically all of them are more soluble in oils and lipids than in water and that when one of these drugs in watery solution meets an oil or lipid, it passes from the water

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to the oil and remains dissolved in it. The same process occurs when these drugs are carried in the blood; they tend to leave the watery plasma and to accumulate in the lipids of the body, and as the nerve cells are richest in lipids, the narcotics accumulate in the brain. This is a purely physical process, and the amount of the drug taken up from the blood is determined by its relative solubility in the lipids and in the blood (*coefficient of partition* between oils and water). This may be expressed as a simple formula: $\frac{\text{solubility in fat}}{\text{solubility in water}}$. According to Meyer's view, the presence of the drugs in the lipids renders these more fluid and thus changes their relations to the other constituents of the cells; this derangement of their normal condition impairs the function of these cells and lessens their activity, that is, causes narcosis. This very attractive theory has been supported by a number of experiments and serves to explain a large number of observations since, in general, the higher the partition coefficient, the greater is the anesthetic property of drugs in an homologous series.

While the experiments of Meyer, Overton, and their followers suffice to show that these physical properties are factors in the narcotic action, there are other determining influences. For when the relative narcotic action of less nearly related bodies is compared, the dependence on the partition co-efficient is less exact; for example, the relative coefficients of partition of alcohol, chloral, and acetone are approximately 1:2:6, but their narcotic action is 1:16:1. There is evidently some unknown factor which plays an important rôle in determining the action besides the solubility coefficient. Other facts indicate that differential solubility in lipids is not an entirely satisfactory explanation of the action of narcotics.

In addition, Clark points out that the action of narcotics on ferments, cells, and living tissues usually shows an approximately linear relation between concentrations and action and that there are striking resemblances between their actions on inorganic catalysts, on purified enzymes, and on living cells. Any theory of narcotic action ought to account for all these phenomena, and differential solubility cannot explain them. He inclines to the opinion, therefore, that narcotics act by covering enzymes or cell surfaces. The effect of such absorption would be to interpose a layer of $CH_3—CH_2$ groups between the active surface and the watery solution, which might effect a barrier to the exchange of molecules between the surface and the solution. This would explain the obvious relations between the biological action of narcotics and their power of lowering surface tension.

Quastel and Wheatley have suggested that, in general, narcotics inhibit the oxidation by the brain of glucose, sodium lactate, and sodium pyruvate with a resultant lowering of available energy to the extent that the cells of the brain cannot accomplish their normal functional activities and anesthesia ensues.

From all the work that has been done on this subject, certain factors emerge. Most workers agree in supposing that the biological effect of narcotics is due to some action on cell surfaces. Many of the biological

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phenomena can be correlated with physical properties of narcotics, but no single or simple property is still adequate to explain all the phenomena or, indeed, is likely to be adequate in view of the extreme complexity of the living cell. The action of narcotics is related to their adsorption on the cell surfaces, and solubility in lipids is an important factor which, however, may be an incidental one.

Various other suggestions have been made as to the nature of narcosis. The old view that it was due to changes in the blood supply and to anemia of the brain has long been abandoned since it was shown that the brain of a frog in which the blood was replaced by saline solution could still be anesthetized. There is no question that the action of narcotics is a direct one on the nervous structures and that the changes in the brain circulation, which are similar to those in normal sleep, are the result and not the cause of the narcotic action.

Certain features of the *chemical* constitution of the members of this group have already been mentioned. Thus it is found that, as a general rule, the higher members of a series are more strongly depressant than the lower, provided they are sufficiently soluble in water to be taken up by the blood and a corresponding increase in the partition coefficient is presented. The increase in hydroxyl groups which augments the solubility in water has the opposite effect, lowering the narcotic action; but if the hydroxyl is substituted by chlorine, the narcotic action returns. The presence of the carboxyl group (COOH) generally prevents any narcotic action, probably because the acids formed circulate as salts, and these cannot penetrate the cells in sufficient concentration. Substitution of halogens for hydrogen increases anesthetic properties; for example, methane (CH_4) is practically not depressant, but if one, two or three of the hydrogen atoms in the molecule be substituted by chlorine, forming CH_3Cl, CH_2Cl_2, and $CHCl_3$, the narcotic power increases with each Cl added.

The chlorine and bromine derivatives of methane are not only more powerful drugs, but also more powerful poisons than the ordinary compounds; much less chloroform is required to anesthetize than methane, but much less is required to kill. In addition, these compounds, especially those containing chlorine, seem to have a more powerful action on the heart and circulation and on the metabolism than the others. In other words, the chlorine bodies have a less specific action on the nerve cells and thus involve a larger number of tissues in their effects. (See Chloroform, p. 269.)

Many methane compounds are not narcotic simply because they contain more active radicals. Thus ethane (C_2H_6) is a member of the narcotic series, but ethyl nitrite ($C_2H_5O—NO$) cannot be classed with it because the —O—NO group has a very powerful and entirely different effect; very small quantities of ethyl nitrite are required to produce the nitrite effect so that the depressant action is pushed into the background. Members of the methane series often lose their depressant action when combined with nitrogen so as to form substituted ammonias. Thus trimethylamine ($N(CH_3)_3$) has no depressant action although each of the methyl radicals alone would possess it. Again, the substitution of a member of the aromatic series for one of the fatty substances sometimes changes the action from that characteristic of the alcohol-chloroform group to that of the benzene series. For example, ether ($C_2H_5—O—C_2H_5$) is one of the most valuable anesthetics, but if one ethyl radical be substituted by phenyl ($C_6H_5—O—C_2H_5$), it loses this property entirely.

While members of this group resemble each other closely in their effects on the central nervous system, they are used for very different purposes in therapeutics and may, therefore, be discussed in three subgroups: (1) alcohol; (2) general anesthetics, and (3) soporifics or hypnotics. It must be recognized, however, that there is no hard and fast line dividing these subgroups for chloral and other hypnotics can give rise to complete anesthesia when administered in large quantities.

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Alcohol

Ethyl Alcohol (CH_3CH_2OH) has been known in an impure form since the earliest times and as far back as the history of medicine extends, has been used in some form by savage as well as by civilized man. Its medicinal reputation has undergone many fluctuations, by many held to be a panacea; by others it has been considered of importance only as a poison.

Alcoholic liquors are generally prepared by the fermentation of sugars, which either exist preformed in the fruits or are derived from starch by a preliminary ferment action. The simple liquors (wines and beers) generally contain only a low percentage of alcohol (2 to 20 per cent), and the stronger preparations (spirits) are prepared from them by distillation, which raises the percentage to 30 to 60 per cent and at the same time removes the non-volatile constituents. Spirits and liquors are not, however, simple mixtures of alcohol and water but contain many other volatile substances.

Action.—The importance of alcohol in medicine depends upon three chief points: (1) its irritant local action; (2) its action on the central nervous system; and (3) its caloric properties.

The **irritant action** is due to the partial precipitation of the proteins of the cells and to its dehydrating property. This is shown by the results of its application to the skin, to wounds, and to mucous membranes. Applied to the skin in sufficient concentration (*e. g.*, 60 to 90 per cent), it produces redness, itching, and a feeling of heat like other volatile and irritant substances such as the volatile oils. Alcohol is however, much less irritant and at the same time more volatile than these so that unless its evaporation is prevented, it may produce a sensation of coolness or cold and have little or no irritant action. This is especially true when dilute alcohol is used since no very distinct appearances of irritation of the skin are produced by solutions under 40 to 50 per cent. On

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ulcers and other unprotected surfaces, the irritant action is much greater, and its application is attended by pain and smarting; the precipitation of the proteins lends alcohol an astringent action in certain concentration (10 to 20 per cent), but if it penetrates deeper, it may destroy the cells, and it then becomes a corrosive until it is diluted by the fluids.

Its effects on mucous membranes are similar to those on wounds. In the mouth, strong alcohol produces a burning, unpleasant sensation which passes to the throat and stomach when it is swallowed, and if used chronically, gastritis usually results. If the concentrated vapor be inhaled, it causes irritation and reflex closure of the glottis. The effects of alcohol on the digestive functions are so important that they will receive further attention (p. 257).

The action of alcohol on the **Nervous Centers** differs a good deal in individuals as well as in the same individual at different times. One person is rendered sentimental, another bellicose, while in a third there may be no appearance of excitement, the first distinct symptom being profound slumber. When drinking is indulged in in company, the excitement stage is a very common phenomenon, but if alcohol is taken without the exhilarating accompaniments of bright lights and exciting companionship, it is much less frequently seen, and the question has therefore arisen how far the environment produces the excitement in alcoholic intoxication. In small quantities, as a rule, it produces a feeling of well-being and good fellowship, along with increased confidence in the powers, mental and physical, of the subject of the experiment. Larger quantities are followed by a certain amount of excitement, marked by laughter, loquacity, and gesticulation. The face becomes flushed and hot, the eyes brighter and livelier; the pulse is accelerated. Even at this stage self-control is partially lost and the will power is weakened. The speech may be brilliant, but it often betrays the speaker; the movements are more lively, but they are often undignified. The loss of self-control is often indicated further by furious outbursts of anger and unreasonableness or by the indulgence in maudlin sentimentality and sensual fancies. The sense of responsibility and the power of discrimination between the trivial and the important are lost, and the individual has no regard for the feelings of others or the ordinary conventions of life. If the bout be further continued, the movements become uncertain, the speech becomes difficult and stammering, the walk becomes a stagger, and a torpid slumber follows (Fig. 11). Often nausea and vomiting set in, although these are entirely absent in some cases. On awakening from slumber, very great depression is generally suffered from together with nausea and vomiting and want of appetite, which may last for several days and is associated with the symptoms of acute gastritis and enteritis.

Very large quantities of alcohol lead to a deep, torpid sleep which eventually passes into total unconsciousness, resembling the condition in chloroform anesthesia; the respiration becomes stertorous and slow, and the face, which has hitherto been flushed, becomes pale or cyanotic. This condition may last for several hours and end in death from failure of the respiration, but in other cases the anesthesia becomes less deep

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and after a very prolonged sleep, the patient recovers. When the stage of anesthesia is reached, it lasts much longer than that produced by chloroform and ether. It is said that persons rarely or never recover if unconsciousness lasts longer than ten to twelve hours after the drinking bout.

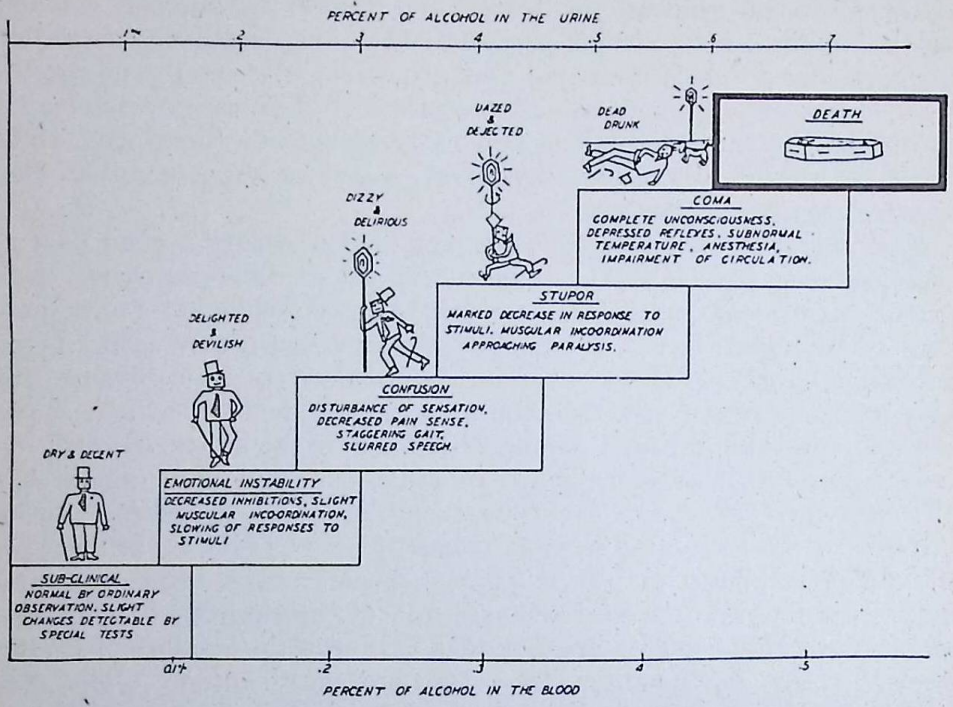

FIG. 11.—Chart showing *behavior reactions* with graduated amounts of alcohol in blood and urine. (From Snyder's Homicide Investigation, 1944. Courtesy of Charles C Thomas, Springfield, Illinois, and Dr. C. W. Muehlberger.)

Individual differences in reactions to alcohol, already mentioned, probably account for the old idea that it primarily stimulated the central nervous system. At the present time, however, no such action is considered since all of its effects may be definitely attributed to its depressant action on the brain. The apparent stimulation may be easily explained as the result of motor and other areas being freed from control by the weakening of the highest functions of the brain—the will and self-restraint. Even the smallest quantities of alcohol tend to lessen the activity of the brain, the drug appearing to act most strongly, and therefore in the smallest quantities, on the most recently acquired faculties to annihilate those qualities that have been built up through education and experience, the power of self-control and the sense of responsibility. The poet Horace recognized release of inhibitions brought about by the depressant action of alcohol when he wrote,

> "What wonders does not wine! It discloses secrets; ratifies and confirms our hopes; thrusts the coward forth to battle; ceases the anxious mind of its burden; instructs in the arts. Whom has not a cheerful glass made eloquent! Whom not quite free and easy from pinching poverty!"

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Again, one only has to recall that in the 1840's "ether frolics" were given for their "exhilarating" effect by men who wished to be relieved of inhibitions. The excitement produced by a general anesthetic is indeed similar to the so-called "stimulating" action of alcohol.

The effect on the *simple reflexes* have been examined carefully by Dodge and Benedict, who find that 30 cc. of alcohol in man lessens the speed and strength of the knee-jerk and of reflex closure of the eyelids; the reflex arc is therefore depressed by alcohol, and there is no question that this action is central in location.

The amount of *work* and *endurance* under alcohol has long been a subject of study. Grubbs and Hitchcock state that muscles are capable of using the energy of ethyl alcohol in performing work. However, the capacity for work depends not so much upon the actual strength of the muscles as upon the condition of the brain. Carefully controlled experiments were performed using the recording ergograph, type setting ability, climbing, and the ability to perform mental gymnastics as criteria to test the validity of the part alcohol plays in increasing physical or mental ability. The results of all tests definitely show that this drug decreases all forms of work. In every instance, it has been conclusively shown that even though the subjects might feel that they were doing more or better physical and mental work, the final results did not confirm the psychological impression. Such experiments are another indication that alcohol is depressant and not a stimulant in any sense of the word. Finally, it is generally recognized that mental and physical equilibrium following the use of alcohol is reinstated only after twelve to twenty-four hours following its ingestion.

The question of the action of small amounts of alcohol upon the central nervous system has assumed great importance in the past few years due to the increased numbers of automobiles and airplanes in use and especially to the higher speeds at which they are driven. Statistics as to the number of accidents directly or indirectly due to alcohol are no oriously unreliable. Obvious drunkenness as manifested by staggering gait and impaired speech is easily recognizable and would rarely cause any great difficulty in ascribing the rôle played by alcohol in a catastrophe. The difficulty is much greater, however, when only small amounts of alcohol have been imbibed—amounts which produce no signs of gross intoxication but which are yet sufficient to render a driver highly dangerous upon the public highway or in the air. An impaired judgment and slowed reflexes may make all the difference between safety and death. The danger is especially great as alcohol disappears from the blood relatively slowly, and its action, therefore, persists much longer than is generally recognized. It should be understood that for such use of alcohol the term "drunkenness" is not applicable but rather "intoxication" or still better the statement that the individual was "under the influence of alcohol."

Blood alcohol per cents may be fairly well coördinated with intoxication (see Fig. 11) As a rule, a 0.20 per cent concentration denotes definite intoxication Many persons, however, are incapable of normal reactions at a level of 0.15 per cent, and even some show evidences of

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intoxication at 0.10 per cent concentrations. Because of these discrepancies, most courts of law recognize definite intoxication to be present if a blood level of 0.20 per cent, a urinary alcohol level of 0.2 per cent, or an exhaled air alcohol concentration of 1.0 mg. per liter exists. The British Committee studying this question concluded that 60 to 90 cc. of whiskey usually affects adversely rapid and accurate coördination and must affect driving capacity even though not causing definite clinical intoxication. In this connection, it can be stated that the average person will show definite signs of marked intoxication after drinking 150 cc. of whiskey or 8 bottles of beer. Naturally, the time involved in consuming these amounts will alter individual reactions as well as blood and urine levels.

Alcohol has been found to cause a prolonged secretion of the *cerebrospinal fluid* and to raise the pressure in the subarachnoid space, and it has been suggested that this may account in part for its after effects which have generally been attributed to gastric disturbance. Such an effect probably explains the cerebral edema or "wet brain" described by the pathologist in a confirmed alcoholic.

The **Respiratory and Circulatory Centers** of the medulla preserve their functions long after the occurrence of complete unconsciousness and the disappearance of the ordinary reflexes. From a practical point of view, the effects of alcohol on respiration are of little importance since changes induced are small and inconstant. The alveolar carbon dioxide tension falls in some cases. This might indicate that the center is more sensitive to the presence of this gas in the blood. However, in many individuals Higgins found no such change, and in any event, the effects in either direction were always slight. Furthermore, in his experiments, the rate of breathing was not altered, and the volume of air breathed per minute was actually lessened. Any stimulation of respiration must be due to a reflex phenomenon arising from irritation of the stomach and not to the center itself. The important thing to remember is that the respiratory center functions perfectly in spite of loss of consciousness and loss of ordinary reflexes.

Circulation.—The pulse is accelerated during the excitement of alcoholic intoxication, but this is due to the increased muscular effort and not to any direct action on the heart since the *pulse* rate is unaltered by alcohol in normal cases, provided that no excitement be produced by the environment. In animals also, the pulse rate is very little altered by alcohol except in very large quantities when it is slowed. Very large quantities of alcohol cause a marked fall in the *arterial tension* through weakening the vasoconstrictor centers and the heart muscle, but the quantities of alcohol required to cause any great fall in blood-pressure are far in excess of those used in therapeutics. The blood-pressure is said to be slightly increased in man in some cases after moderate quantities of alcohol (15 to 30 cc.), but in at least an equal number of observations it was found to be slightly reduced, and in many no definite change could be made out. Grollman showed that when moderate amounts (30 cc.) of alcohol in a dil ted form are given occasional drinkers, there is a slight rise in pulse rate coming on in from

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fifteen to thirty minutes and not dependent upon psychic factors which might produce such changes in non-drinkers immediately after alcohol has been taken. In moderate drinkers, slightly larger amounts (35 cc. or more) caused appreciable increases in both blood-pressure and in cardiac output. Alcohol is believed by some to augment the strength of the heart, but the change is small in extent and inconstant in its appearance. Peters *et al.* found that blood concentrations (less than 0.4 per cent) would actually decrease the capacity for the heart to function properly. Larger quantities affect the heart in the same way as ether and chloroform, weakening the auricular and later the ventricular systole and inducing dilatation and slowing of both chambers. The action of alcohol on the heart is much less, however, than that of chloroform and ether, much more being required to arrest the frog's heart, and the mammalian heart continues to beat when perfused with 2 per cent alcohol.

The flushing of the skin which occurs in alcoholic intoxication indicates dilation of the skin vessels, giving a false impression of increased warmth. These seems to arise from central vasomotor action, but whether it is due to direct stimulation of the centers or arises from a reflex from the stomach is not yet determined. Alcohol is not to be considered a predisposing cause of angina pectoris since it dilates coronary arteries and in moderate doses is beneficial (White and Sharber).

On the whole, the action on the circulation of small quantities of alcohol (15 to 30 cc.) may be favorable in some conditions but is so slight and inconstant that it is impossible to regard it as a basis on which serious therapeutics can be founded. The slowing of the heart which often follows the administration of alcohol in fever would seem due rather to its diminishing the cerebral excitement than to its direct action on the heart.

Alcohol has little effect on **Muscle** or on peripheral **Nerves** and any increase in muscular work accomplished is probably due to lessened consciousness of fatigue plus improvement in the circulation caused by peripheral vasodilatation and not to utilization of the drug by muscle tissue as suggested by early workers in this field. Large doses definitely decrease muscular work through central depression.

The effect of alcohol on the **Digestion** has been the subject of many investigations, both from the clinical and the experimental point of view (Beazell and Ivy). There exists a widespread belief in both lay and medical circles that small quantities of alcohol taken before a meal increase the appetite while after food they accelerate the digestion. It is obvious that alcohol may affect digestion either by altering the activity of the ferments in the digestive canal or by altering the secretion, movement, or absorption of the stomach and intestine. In concentrations under 20 per cent, alcohol may stimulate the flow of the *pancreatic juice*. When somewhat larger amounts are added, the peptic activity of gastric juice is greatly reduced, and even small quantities of the ordinary wines and beers have this detrimental effect. In the latter instance, the concentration of alcohol is not a factor, but instead certain organic by-products resulting from their manufacture are the responsible

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agents. Excessive amounts of alcohol decrease the secretion of intestinal and pancreatic juices as well.

The presence of alcohol in the mouth causes a very appreciable increase in the secretion of the *saliva*, presumably by reflex action, and a similar increase in the acidity of the gastric juice may perhaps follow from its local irritant action on the stomach. Apart from this, it appears to exert a specific action on the secretion after its absorption into the circulation. When it is injected into the rectum, a profuse secretion from the gastric mucous membrane follows, and when part of the stomach is isolated from the rest of the organ so that alcohol given by the mouth fails to enter it, this part still shares in the secretion, but the pepsin secretion is not correspondingly augmented. It has been further demonstrated that the absorption of fluids from the stomach and bowel is accelerated by the addition of alcohol while the movements of the stomach are unchanged or diminished by moderate quantities.

In summary, dilute concentrations of alcohol in moderate amounts do not interfere with digestion. Small quantities of it ingested by persons who enjoy the taste of the beverage actually improves digestion. On the other hand, excessive amounts often cause nausea and vomiting, increased mucous secretion, gastritis, and even enteritis due to its local irritant and dehydrating properties.

Absorption and Excretion.—Alcohol is absorbed rapidly, about 20 per cent of that ingested being taken up in the stomach and 80 per cent in the small intestine. The rate of absorption varies with the concentration, strong alcohol appearing more quickly in the blood than the same amount in greater dilution; food delays the absorption when taken at the same time, especially if it contains much fat (Mellanby). The concentration of alcohol in the blood reaches its maximum about two hours after it is swallowed, and then the level falls slowly, the amount in the blood being determined by the balance between that which is being absorbed and the amount undergoing oxidation and excretion. However, it requires a longer period of time for the brain to acquire a peak level of alcohol and longer for it to lose its final concentration. Harger and Hulpieu found that 25 per cent alcohol given by mouth to dogs is absorbed very quickly. They state that 89 per cent was absorbed in the first hour and that absorption was practically complete in two hours. The course of intoxication follows the curve of the concentration in the blood fairly closely.

Alcohol is found in largest proportions in the *blood plasma*, which contains about twice as much as the *corpuscles;* Gréhant found as much as 0.6 per cent in the blood of animals, but more than this was inevitably fatal. Traces remain in the blood for about twenty-four hours, but over 90 per cent of that ingested is oxidized in that time with a resultant release in energy and the formation of carbon dioxide and water.

The *rate* of oxidation of the alcohol in the body is proportional to the amount which is present in the body. Carpenter and Lee have shown that metabolism of alcohol as indicated by the course of the respiratory quotients and the oxygen absorption proceeded at about the same rate irrespective of whether the subject was at rest or engaged in muscular

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activity. These same authors showed that muscular work did not appreciably alter the concentration in urine, blood, or in expired air. Furthermore, although they noted that the amount of alcohol eliminated by respiration was about twice as much during work as during rest, that this only amounted to 0.4 to 0.7 per cent of the amount ingested at rest and from 0.9 to 1.6 per cent of the amount ingested in the working experiments. Hence, work played a negligible rôle in reducing the amount of alcohol in the body. The techniques employed in these well-controlled experiments should convince the most doubtful that it is not possible to increase markedly the oxidation of alcohol.

The alcohol which escapes combustion in the tissues is excreted by the kidneys unchanged and by the lungs, but this is usually less than about 5 per cent of the total amount ingested. The lungs excrete very little alcohol—0.5 to 2 per cent. It is doubtful if artificial hyperpnea induced by carbon dioxide is of any significant value in hastening excretion via the respiratory system. At least in the treatment of alcoholic intoxication, exact studies have failed to indicate any decrease in alcohol concentration due to the inhalation of carbon dioxide.

The amount of alcohol excreted by the kidneys varies with the amount of urine, and the percentage of alcohol taken which is lost through the kidneys depends upon the amount of urine passed. During sixteen hours following the administration of alcohol to dogs, approximately 2 to 4 per cent of the total amount taken is eliminated in the urine, the variation being due to the rate of urinary secretion. Haggard and Greenberg found that the concentration of alcohol in the urine in relation to that in the arterial blood corresponded closely to the relative solubility of alcohol in blood and in urine, and they conclude, therefore, that alcohol passes through the kidney by simple diffusion. More alcohol is excreted when it is taken on an empty stomach than when it is taken with food, but even in these conditions over 90 per cent undergoes complete combustion in the tissues.

Traces are sometimes found in the sweat and milk, but there is no foundation for the legend that children may be intoxicated or acquire a taste for strong drink from the alcohol absorbed in the milk of a drunken mother or wet-nurse. Furthermore, the amount and quality of the milk are unaffected by the administration of alcohol (Rosemann). Minute amounts of alcohol are eliminated in some quantity in the bile but are not absorbed in the intestine.

Is Alcohol a Food?—It has been shown that in man only 5 per cent or less of the ingested alcohol is excreted while the rest of that absorbed from the stomach and bowel, amounting to over 90 per cent, undergoes combustion in the tissues. In this process, alcohol furnishes energy to the body and, therefore, is technically a food, but this does not imply that it is an advisable food in all conditions. Experiments in which the carbon dioxide excretion was measured under alcohol show that no more energy is required for its absorption than for that of other foods and that alcohol taken in addition to the ordinary food undergoes oxidation instead of carbohydrate and fat, which in turn are used to build up reserves of energy in the body. Alcohol itself cannot be stored in the

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tissues and is, therefore, utilized in place of the carbohydrate, which is deposited as glycogen; an increase in the fat of the tissues has been shown to occur in animals treated with alcohol and is a common observation in man (Tögel, Brezina, and Durig). Alcohol, therefore, acts as a substitute for carbohydrates and fat in the food and is utilized like them for the production of heat and work; a usual drink of whiskey will supply about 70 calories.

It has long been recognized that when insufficient fat and carbohydrate is supplied to the body, the proteins are drawn upon to make good the deficiency and the nitrogen eliminated rises accordingly. On the other hand, when the fats and carbohydrates of the food are increased, the organism economizes its protein and the nitrogen tends to fall. This is the most accurate method of testing the food value of non-nitrogenous substances, and alcohol has been the subject of a number of such investigations (Neumann, Atwater and Benedict, Rosemann). The results may be summarized as follows: Alcohol corrected increased destruction of proteins when it was substituted for a deficient amount of fat in the diet. When alcohol was given in addition to a sufficient fat intake, nitrogen excretion markedly fell, indicating a sparing action on proteins similar to the effect of other non-nitrogenous substances. (See Fig. 12.)

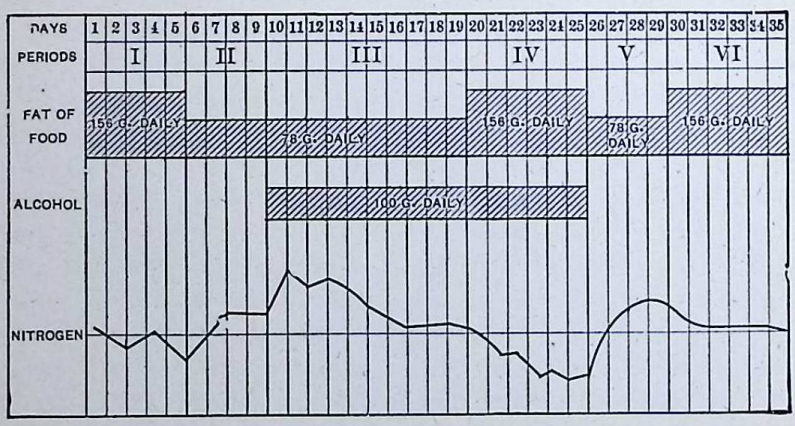

FIG. 12.—The effect of alcohol on nitrogen elimination. The wave-line represents the nitrogen excreted. It rises rapidly in the second period when the fat of the food was reduced to one-half, but soon falls in the third period where alcohol was substituted. 100 Grams of alcohol is chemically equivalent to 78 grams of fat. (After Neumann.)

Metabolism.—A decrease in general metabolic energy results only when very large quantities of alcohol are taken and depression and sleep follow. This effect is due to decreased muscular movement. The opposite effect is seen during the excitement phase. Lolli *et al.* found that alcohol causes an increase in extracellular water in fasting animals. Thirst was not relieved by water in amounts equal to those lost in diuresis.

Effects on Growth and Progeny.—Heredity.—Much has been written on the subject of heredity and alcohol. Stockard's animal experiments do not show that alcohol causes deterioration in several generations of

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offsprings whose parents were subjected to alcohol. He believes, therefore, that a child does not inherit alcoholism nor are children of alcoholics necessarily more prone to epilepsy, mental deficiencies, and the like unless their parents were mentally unbalanced. It should be emphasized that while daily moderate amounts of alcohol do not appear injurious to human beings, excessive amounts of spirits decrease life expectancy.

Hepatotoxic Effects.—Long continued excessive use of alcohol will cause a serious disturbance of liver function and will probably damage the hepatic parenchyma when existing disease is present. Without such a preëxistence of disease, there is doubt as to the exact effect of alcohol on the hepatic cell. Newman *et al.* have shown that ethyl alcohol is metabolized directly by the liver and exerts a depressing effect on its functional activities as indicated by a decrease in oxygen consumption, an increase in blood lactic acid, and a decrease in liver glycogen of as much as 45 per cent. Since the liver may be the chief site for the initial oxidation of alcohol, it is important to stress the rôle that insulin plays in this metabolic process. Recent work would indicate that insulin markedly influences the oxidation of alcohol in the liver. Finally, Goldfarb, Bowman, and Parker have shown that increased utilization of glucose under the influence of injected insulin also favors a more rapid and complete oxidation of alcohol in the liver. In addition, Connor has been able at the autopsy table to trace all stages of progression from the large, smooth, fatty liver, which is the most constant anatomic finding in chronic alcoholism, through a hypertrophic stage of cirrhosis to eventual atrophy. The authors agree with Newman that there must be a direct metabolic effect of alcohol on the liver.

Moon is of the opinion, as are the vast majority of pathologists, that no creditable evidence for experimental cirrhosis of the liver due to alcohol has ever been produced. It is true that when alcohol is given to dogs along with a high fat diet a fatty liver results much more quickly than though the alcohol had been omitted; however, no true cirrhosis developed. Rosenthal found that the administration of alcohol by mouth in doses of 2 cc. per kilo of body weight rendered the liver more susceptible to the action of chloroform since most of the dogs so treated died after a two-hour chloroform anesthesia following recovery while the controls recovered and lived. These findings are in agreement with those described by MacNider who found in dogs which had been intoxicated with alcohol for twelve hours an increased retention of phenoltetrachlorphthalein indicative of liver injury, but recovery was complete in from two to three days.

The multitude of toxic effects attributed to alcohol in the past are no longer believed to be due to alcohol itself but result rather from the dietary deficiencies to which the chronic drinker is subjected. Thus the cirrhosis of the liver, peripheral neuritis, and myocardial dilatation common in the drunkard are now believed to be manifestations of thiamin deficiency rather than results of any direct toxic effect of alcohol.

Influence on Infection.—There is no proof that alcohol directly decreases the resistance of an individual to infection. Experiments reporting such effects in the human and in animals are not clear-cut, and statistically

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the differences are never significant. Consequently, while alcohol has often been claimed as a cause for lowered resistance, any decrease in the ability to combat infection is due entirely to the general physical disability seen in chronic alcoholics.

The **Temperature** of the body falls somewhat after the administration of alcohol, but this is not due to any diminution in the oxidation and in the heat formed but to the greater output of heat from the dilation of the skin vessels. The fall in temperature is comparatively slight, seldom being more than $\frac{1}{4}$ to 1° C., but it would seem that exposure to cold causes a greater fall in the temperature after alcohol than in normal conditions; this is perhaps due to the temperature-regulating mechanism being rendered less sensitive by alcohol.

The fall in temperature produced by alcohol is generally accompanied by a feeling of heat, and a thermometer applied to the skin may actually show a rise of several degrees because more blood flows through the dilated vessels. If much excitement and movement follow the ingestion of alcohol, no fall in the temperature may result, the increased heat formed during the movement compensating for the increased output, and in some cases, a rise of temperature occurs from the same cause. Very large quantities of alcohol may lead to a fall in temperature of 3 to 5° C., owing in part to the lessened movements during unconsciousness.

Repeated doses of alcohol produce **Tolerance** which, although not so great as that acquired for morphine and nicotine, involves the prescription of double or triple doses in persons addicted to drinking, but this amount cannot easily be increased even in tolerant individuals. The explanation for tolerance to alcohol is not clearly understood. It may arise in part from the tissues acquiring an increased capacity to oxidize alcohol; and as oxidation begins almost as soon as absorption, a large quantity of alcohol taken by an habitual drinker may not lead to the accumulation in the blood of a sufficient quantity to induce symptoms of intoxication. In addition to this factor, the brain may react less than normally for Schweisheimer finds that a given concentration of alcohol in the blood induces greater intoxication in an abstinent than in a tolerant person. Finally, no good proof exists that a tolerant person excretes more or less alcohol than a non-tolerant individual. The close relationship between alcohol and the narcotics of the fatty series is indicated by the fact that much more chloroform or ether than usual is required to anesthetize persons in whom a tolerance for alcohol has been established.

Although alcohol seems to increase the **Urine** to some extent, it cannot be said to be a powerful diuretic in itself, and the diuresis may be explained in large part by the quantities of fluid taken with the alcohol and by the accelerated absorption from the alimentary tract. Some of the spirituous liquors, such as gin, produce a larger secretion of the urine, but this is due to their other constituents and not to the alcohol.

MacNider has compared the effects of ethyl alcohol and of an alcoholic distillate made from meal and sugar or molasses upon the kidneys of normal and nephropathic dogs. He found that alcohol has little effect upon the kidneys of

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normal dogs but that nephropathic animals were more susceptible, the alcohol causing an increased urine formation and a slight increase in the albumin present in the urine. The fresh distillates were much more toxic, producing in normal animals an increase in urine with large amounts of albumin, the glomeruli showing evidence of fatty changes. In nephropathic animals the increase in urine was only slight and was followed soon by reduction in the quantity and finally by anuria. In the early stages the albumin in the urine was much increased and there were numerous casts. The greater toxicity of the fermented mixtures was evidently not due to the ethyl alcohol contained but to some other unknown substance.

Alcohol is generally credited with **Aphrodisiac Powers**, that is, with increasing sexual desire, although no less an authority than Shakespeare states that it prevents the consummation of sexual intercourse. The unquestionable tendency toward sexual excess observed in intoxication is due not to any effects on the generative organs but to the loss of self-control from the cerebral action of the poison.

Alcohol is not a potent **Antiseptic**, for while the growth of some bacteria is delayed somewhat in a 1 to 1,000 solution, many grow abundantly in 4 per cent alcohol and some in even stronger solutions. However, when used in proper concentrations, it is useful as an external skin antiseptic and for partial sterilization of instruments. (See Alcohol as an Antiseptic, p. 778.) Its disinfectant action has been the subject of a number of researches and has been found to vary with the conditions. It must be emphasized that alcohol is useless as an antiseptic unless it is used in a 70 per cent by weight concentration. Solutions containing less than this amount possess no bacteriostatic effect, and those containing higher concentrations are of little benefit since they fix the proteins of the skin before they penetrate and attack bacteria.

The signs and symptoms of **Acute Alcoholic Intoxication** are usually unmistakable. However, this form of poisoning may be confused with acute barbiturate mania and with the dizziness elicited by some of the sulfonamides. One should always determine blood, urine, and exhaled air levels since failure to note an alcoholic odor of the breath does not rule out the possibility of alcoholic poisoning. When very large amounts have been ingested, the patient appears to be anesthetized.

In regard to the **Habitual Use of Alcohol** by healthy persons, all authorities agree that it is a luxury, that it is entirely unnecessary for the growth and maintenance of the body, and that it neither promotes greater healthfulness nor in any way retards the onset of disease. It is true that it is utilized by the body as a food, but its value as such is limited because only small quantities can be taken without disturbance of the nervous system. At the same time, it is difficult to prove that the moderate use of alcohol is injurious for when taken after work it seems to cause no impairment of the capacity for work the next day and often seems to remove the sense of fatigue. In many it undoubtedly promotes happiness and allays the worries and anxieties of life.

The habitual indulgence in alcohol to excess often leads to a chronic alcohol habit. The continual user then becomes a drunkard since he finds that under alcohol his consciousness of unhappiness is numbed and all depressions disappear. In this way he loses the sense of degrada-

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tion and remorse which possesses him when sober. The depression returns in exaggerated form after the effects of the drug have passed off, but it can be removed again by the same means, and in this way the habit is formed, each successive dose being rendered necessary by the depression produced by its predecessor. This descent into chronic drunkenness is facilitated by the lessening of the self-control, owing to the action of alcohol on the brain. The victim may form the best of resolutions, but his impaired will power and self-control are unable to carry them out.

The earliest symptoms of **Chronic Alcoholism** are generally observed in the stomach, throat, and larynx and consist of a chronic catarrh, which is often accompanied by skin affections such as injection of the cutaneous vessels (especially those of the face), acne, or pustular eruptions. Fatty degeneration occurs in the liver especially and is said to be accompanied by a marked decrease in the lecithin and other lipids of the cells. Cirrhosis of the liver is not now believed to be the direct result of alcoholism. (*Cf.*, p. 261.) Fatty degeneration is also found in the arterial walls throughout the body, and the heart has been reported to undergo more or less fatty change accompanied by dilatation and weakness. Of greater importance, however, are the alterations of the central nervous system which lead to impairment of memory, self-control, and other higher mental processes. Tremor, convulsive attacks, hallucinations, and mania not uncommonly follow once the disease is well established. A form of amblyopia commencing with atrophy of the retinal ganglion cells and later extending to the fibers of the optic nerve has recently received some attention; it is much more readily elicited by methyl than by ethyl alcohol. The neuritic symptoms occurring in chronic alcoholism resemble those seen in beri-beri and are due to vitamin B_1 deficiency. Such patients may rapidly improve when this deficiency is supplied even though their alcohol intake may still be continued.

In any instance, a chronic alcoholic should be looked upon as one suffering from a real disease, since like morphine addiction, there is little else to be seen than the alcohol habit itself. Finally, chronic alcoholics are not necessarily mentally defective—many are brilliant and successful individuals during abstinence.

A characteristic result of chronic alcoholism is **Delirium Tremens**, an acute attack of insanity which is liable to occur after any shock, such as hemorrhage or acute disease, but which is said to be also produced by the sudden withdrawal of alcohol, especially undiluted spirits, and sometimes occurs without any apparent immediate cause. It is characterized by tremor, perspiration, sleeplessness, fear, excitement, and hallucinations of the various senses, which differ from many other hallucinations of insanity in consisting of the multiple appearance of the same object. These objects are often animals, such as snakes, rats, dogs, but the hallucinations are not confined to those of sight, for whispering voices are complained of not infrequently. Paraldehyde administered rectally in doses of 15 to 30 cc. is recommended for the control of fear and mania.

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The **Treatment of Acute Alcoholic Intoxication** is to evacuate the stomach by means of the stomach tube or by the injection of apomorphine (5 mg.). The patient ought to be put to bed and kept warm as there is a tendency to a marked fall in the body temperature. Cold may be applied to the head in the form of ice-bags. In cases of extremely deep unconsciousness, stimulants, such as caffeine rectally in the form of "black coffee" or as an injection of caffeine and sodium benzoate (0.5 gram) or strychnine injections (2 to 4 mg.) and ephedrine in 25 mg. doses may be employed and, as a last resort, artificial respiration. In extreme cases, the inhalation of a mixture of carbon dioxide, 10 per cent, and oxygen, 90 per cent, has been recommended. It is claimed for this method of treatment that patients receiving it breathe more deeply and regularly and that cyanosis disappears.

Chronic alcoholism is best treated by gradual withdrawal of the poison as the immediate stoppage may lead to delirium tremens. Withdrawal alone is not enough, however, since environmental and personality adjustments must be made and hence the rehabilitation of an alcoholic is very important. Best results are often obtained in some retreat or hospital, but the patient should not be considered a "mental case" lest all treatment go for nought. Most drugs are useless except where sedation is necessary, and chloral hydrate in oral doses of 1 gram and paraldehyde, 4 to 8 cc., are indicated. Another method of treatment, which appears to be successful in some cases, is the addition of nauseating drugs, such as ipecacuanha or apomorphine, to the alcohol which is supplied to the patient. The association of nausea with liquor eventually becomes so strong that alcohol in any form becomes distasteful. Any organic lesions must be treated individually, and symptomatic treatment at all times is paramount in this condition. The treatment of delirium tremens has already been discussed.

Therapeutic Uses.—Alcohol is used *externally* in dilute solution, 25 to 30 per cent, as a cooling application to the skin. In preventing bedsores, in which it is often applied in order to harden the epidermis, a concentration of 50 per cent is recommended. As an antiseptic applied to the skin, it should be used only as a 70 per cent by weight solution. When it is kept from evaporation, it acts as a rubefacient and irritant. Its use to wash the skin and hands before operations arises from its power of cleansing the skin and removing the oils and fats as well as from its disinfectant action. Alcohol is useful *locally* in the treatment of phenol burns, but it should be washed off immediately with water, else it does more harm than good. It is contraindicated in a lavage after phenol has been swallowed. Strong alcohol (80 per cent or more) may be *injected* into nerves or ganglia for the relief of neuralgia, sciatica, and similar disorders and leads to degeneration of the nerve fibers and paralysis of sensation and motion which lasts until the nerve fibers are regenerated after several months. The pain disappears until this restoration is complete and sometimes permanently. The local nerve destruction arises from the precipitation of proteins and the solution of lipids.

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Its use in *intraspinal* injection for persistent pain in advanced carcinoma is best discussed in appropriate texts on surgery.

The indications for the *internal* use of alcohol are ill defined, and cases which one physician would treat with alcohol often seem to progress as favorably without it in the hands of another. It has been prescribed very largely in the past as a "stimulant" under the impression that it increases the activity of the circulation, respiration, and other functions of the body. The action which lends alcohol its value in therapeutics is not its stimulant but its narcotic action, which allays the anxiety and distress of the patient, promotes rest and sleep, and thus aids toward healing, or at the worst renders illness more tolerable. Small quantities of other narcotics might be substituted for alcohol, but perhaps none of them excel it in producing that spirit of hopefulness and restful confidence which contributes so much to recovery.

If the patient enjoys the taste of wine, a glassful before dinner often improves the appetite and may be especially beneficial in persons recovering from a debilitating disease accompanied with marked loss of appetite. If a similar patient suffers from insomnia, then a "nightcap" of a pleasant tasting alcoholic beverage is preferred to any of the hypnotics, such as chloral or a barbiturate.

In the treatment of *hemorrhage, shock* and sudden *cardiac arrest,* alcohol is of little, if any, value.

In *acute fevers,* alcohol is of no value unless it is given in lieu of hypnotics since its only effect is to quiet and relax the patient through its central depressant action.

Alcohol should not be prescribed for internal use by the physician if he feels that the patient may develop a habit. Alcohol is definitely contraindicated in renal and hepatic disease, in gastric and duodenal ulcer, in ulcerative colitis, and in epilepsy. Since alcohol increases the secretion of acid by the stomach, it is sometimes used as a clinical test of gastric secretion. For this purpose 50 cc. of a 7 per cent solution are administered orally.

Alcohol is used extensively in *medicinal preparations* as a vehicle in the form of elixirs and tinctures. In addition, fluid extracts contain appreciable amounts of alcohol. It is a wise physician who prescribes only the minimal amount of alcohol in his prescriptions for patients since many alcohol habits have been started by the taking of medicines which were highly alcoholic.

The use of alcohol as a *general anesthetic* has also been proposed (Verkhovskaya). Patients were given morphine preoperatively one-half hour before the alcohol was administered. In the operating room, a mixture of one part of 95 per cent alcohol with two parts of 5 per cent glucose was administered by intravenous infusion over a period of fifteen to twenty minutes. The average dose for complete narcosis was found to be 2 to 2.5 cc. of alcohol per kilogram of body weight. As a rule, sleep begins after 40 to 60 cc. of alcohol have been introduced. When deep anesthesia has set in, the vein is flushed with 30 to 40 cc. of an isotonic solution of sodium chloride to prevent possible thrombo-

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phlebitis. Sleep lasts from two to five hours; upon awakening, the patient is often irrational and requires special attention.

Methyl Alcohol, or wood alcohol, has assumed importance from a large number of cases of poisoning having occurred from its being substituted for ethyl alcohol as an intoxicant, from its presence in proprietary remedies, or from its use in the industries. In animal experiments, it is found that, given in single doses, it is slightly less poisonous than ethyl alcohol, the action coming on somewhat more slowly but lasting a longer time; the symptoms of gastric irritation are generally more marked than those induced by ethyl alcohol, and very often some convulsive movements are observed. When the administration is repeated, methyl alcohol is found much more poisonous than ethyl, and this arises from its slower oxidation and consequent prolonged action. Thus it has been shown that when equal amounts of methyl and ethyl alcohol are administered to animals, over one-third of the methyl alcohol can be found in the tissues for forty-eight hours, while of the ethyl alcohol only about one-tenth remains after fifteen hours. About 40 per cent of the methyl alcohol is oxidized in forty-eight hours, while 20 per cent escapes in the breath and 3 per cent in the urine. Pohl has pointed out that while ethyl alcohol undergoes complete combustion in the tissues, methyl alcohol is slowly oxidized to formic acid, most of which is excreted in the urine.

In man the symptoms of wood alcohol poisoning differ from those of ordinary spirits in the more marked abdominal pain together with nausea and vomiting, muscular weakness, and defective cardiac action with coma. Delirium may be much more intense and persistent than that seen in intoxication with ethyl alcohol. In a considerable number of cases death has followed from a single dose smaller than would have been fatal had ethyl alcohol been swallowed, and in some cases total and permanent blindness has followed or accompanied recovery. This condition is more often the result of repeated ingestion of the alcohol, however, and it is due to optic neuritis and subsequent complete optic atrophy. The large number of cases of blindness or fatal intoxication which have been reported demonstrate clearly the danger incurred in the use of this poison internally or even externally or by inhalation of its vapor. Optic atrophy has been induced in animals repeatedly by the administration of wood alcohol while it is hardly liable to occur from ethyl alcohol.

Even though the toxic symptoms of methyl alcohol poisoning are often delayed, no very good form of treatment was known until recently. Chew *et al.* have pointed out that the chief effect of methyl alcohol is a profound alteration in metabolism resulting in acidosis. He and his co-workers have reported excellent results in twenty-six patients following treatment with sodium lactate intravenously plus 4 grams of sodium bicarbonate orally every fifteen minutes for four doses, repeatnig the alkali until the plasma carbon dioxide combining power was 40 to 50 volumes per cent and the urine had a pH of 7.8.

The other *alcohols* are mainly of interest as impurities of the preparations of ethyl alcohol. They all resemble it in their general effects

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but differ from it in toxicity; propyl alcohol is more powerful than ethyl, butyl than propyl, and amyl than any of them. Amyl alcohol, or fusel oil, is present in small quantity in most forms of spirits. It resembles ethyl alcohol in general, but is more irritant locally and is believed by some authorities to have more deleterious effects in chronic poisoning than pure ethyl alcohol. This is not based on any very satisfactory evidence, however, and all the characteristic symptoms of chronic alcoholism have been produced in animals by pure ethyl alcohol. Furfurol is also present in many forms of spirits but in such small quantities that it does not play any rôle in the symptoms induced by them.

Preparations

Alcohol, ethanol, ethyl alcohol, spiritus vini rectifactus (U. S. P.), alcohol (95 per cent), (B. P.), (C_2H_6O). It contains not less than 92.3 per cent by weight corresponding to 94.9 per cent by volume (U. S. P.), and not more than 95.2 per cent by volume and not less than 92 per cent by weight (B. P.). It is a transparent, colorless, mobile and volatile liquid (U. S. P., B. P.).

Alcohol Dehydratum, dehydrated alcohol (U. S. P., B. P.), containing not less than 99 per cent by weight of C_2H_5OH (U. S. P.), and not less than 99 per cent by weight of C_2H_6O (B. P.).

Alcohol Dilutum, diluted alcohol (U. S. P.), a mixture of alcohol and water containing not less than 41 per cent and not more than 42 per cent by weight of C_2H_5OH. In addition there are also included eight dilute alcohols ranging in strength from 90 to 20 per cent alcohol (B. P.).

Elixir Aromaticum, aromatic elixir (U. S. P.), absolute alcohol content about 23 per cent.

Spiritus Frumenti, whiskey (U. S. P.), an alcoholic liquid obtained by the distillation of the fermented mash or wholly or partly malted cereal grains and containing not more than 53 per cent by volume of C_2H_5OH.

Spiritus Methylatus Industrialis, industrial methylated spirit (B. P.), contains 19 volumes of alcohol (95 per cent) with 1 volume of approved wood naphtha known as "66 O. P. Industrial Methylated Spirits."

Spiritus Vini Vitis, brandy (U. S. P.), an alcoholic liquid obtained by the distillation of the fermented juice of sound ripe grapes and containing not more than 54 per cent by volume of C_2H_5OH.

The *wines* and *beers* are much weaker preparations of alcohol, the light wines (hock and claret) containing about 6 to 8 per cent ethyl alcohol, while in sherry and port it may amount to 15 to 20 per cent. *Champagne* and the other sparkling wines contain large quantities of carbonic acid, which acts as a stimulant to the gastric mucous membrane.

The beers generally contain a comparatively small percentage of alcohol (3 to 5 per cent), along with a large amount of solids. These solids consist mainly of dextrin, sugar, and other starch products, which retard the absorption of the fluid, but are of some value as foods. The hops added in the preparation have probably no action save as bitter stomachics. The alcohol of beer is comparatively slowly absorbed, owing to the colloid constituents. When beers and porter do not derange the digestion, they are the most nutritive of all the alcoholic preparations owing to the large amount of carbohydrates they contain.

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II. GENERAL ANESTHETICS

1. Ether and Chloroform

The term *general anesthetics* is employed to indicate substances used to produce unconsciousness sufficiently complete to allow of surgical operations being performed. In the history of medicine, there are repeated obscure allusions to substances used for this purpose, but it was not until the end of the first half of the nineteenth century that the era of surgical anesthesia really opened. In 1799, Davy advised the use of nitrous oxide as an anesthetic, but no practical use was made of his suggestion, and Wells may be said to have rediscovered this property of the gas in 1844, though his efforts to introduce it into general use met with no greater success than Davy's. Long first used ether in 1842 in surgical operations but did not give any publicity to his discovery. The honor of demonstrating publicly the practical use of ether in surgery must be awarded to Morton (1846). Credit must also be given to Jackson since Morton consulted him about ether before he used it publicly. In 1847, Simpson introduced chloroform to the medical profession as a substitute for ether, over which he supposed it to possess

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several advantages. Its pharmacological action had been examined some months earlier by Flourens, but Simpson appears to have made his investigations quite independently. Chloroform soon ousted ether in popular favor in Europe, but in America a considerable number of surgeons continued to use ether. The increasing number of accidents in chloroform anesthesia caused a reaction to set in in favor of ether which is now far more extensively used than chloroform throughout the world.

These anesthetics are invariably given by inhalation and not by the stomach as it is found that the exact depth of the narcosis can be much more easily controlled by the former method. Both the absorption and excretion of these drugs occur almost entirely by the lungs, according to the ordinary physical laws of the absorption of gases by fluids. The more concentrated the vapor of chloroform in the lungs, the greater is the quantity absorbed into the blood and the deeper the narcosis. By regulating the proportion of the vapors in the air inhaled, therefore, an anesthesia of any desired depth may be induced. The degree of narcosis and of danger is not indicated so much by the actual amount of the anesthetic which has been used as by the concentration of the vapors which have been inhaled and the consequent concentration in the blood.

Symptoms.[1]—The action of ether and chloroform may be divided into *four* stages: (1) that of imperfect consciousness and analgesia; (2) that of excitement and delirium; (3) that of complete unconsciousness or surgical anesthesia; (4) that of overdosage and medullary paralysis. (See table on p. 271.)

The *first effect* of their application is a feeling of asphyxia, which is especially marked in the case of ether, and of warmth of the face and head and eventually of the whole body. The senses become less acute, the patient seeming to see only through a veil of mist, and the voices of those in the immediate neighborhood appearing to come from a distance. Ringing, hissing, and roaring in the ears and a feeling of stiffness and of inability to move the limbs herald the approach of unconsciousness. With the exception of the first feeling of suffocation, the sensations are generally pleasant. During this stage the face is generally flushed, the pupils enlarged, the pulse is somewhat accelerated, and the blood-pressure is elevated. The respiration may be rendered

[1] The poet, Henley, has given the following description of his sensations under chloroform in Lister's wards in the Royal Infirmary, Edinburgh:

Then they bid you close your eyelids,
And they mask you with a napkin,
And the anæsthetic reaches
Hot and subtle through your being.

And you gasp and reel and shudder
In a rushing, swaying rapture,
While the voices at your elbow
Fade—receding—fainter—farther.

Lights about you shower and tumble,
And your blood seems crystallizing—
Edged and vibrant, yet within you
Racked and hurried back and forward.

Then the lights grow fast and furious,
And you hear a noise of waters,
And you wrestle, blind and dizzy,
In an agony of effort.

Till a sudden lull accepts you,
And you sound an utter darkness—
And awaken . . . with a struggle . . .
On a hushed, attentive audience.

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irregular by the sense of suffocation or may be slightly quickened. Even at this early stage sensation is blunted.

CHIEF SIGNS OF ANESTHESIA

	Respiration: Inter Costal	Respiration: Diaphragm	Color of Face	Muscular Relaxation	Pupil size (Normal & Equal to medium size)	Eye Reflexes	Pulse	Blood Pressure	Depths Needed for Surgery	Temperature	Miscellaneous
Stage 1			+ + Flushing Pale? with Chloroform	Little Change		Intact.	Increased + +	Elevated +	Normal Delivery	Normal	Coughing
Stage 11			+ + + or More. Flushing	Decreased		Eyelid Absent	Increased + + +	Elevated + +	Not Possible to Operate	Temporary Elevation	Swallowing
Stage 111 Plane 1.			+ + + Flushing. Some Cynosis with Ether	Incomplete		All Absent	Normal	Normal	Most Eye ear and Nose Work	Gradually	Eye ball fixed
Plane 2.			+ + Flushing	Almost Complete		All Absent	Normal	Normal	Nephrectomy Appendectomy Cholecystectomy		No respiratory reflex from Skin Incision
Plane 3.			+ Flushing	Complete		All Absent	Increased +	Elevated and then Decreased +	Gastrectomy	As much as 1.5° degrees C.	
Plane 4.			± Flushing also Cynosis	Beginning Paralysis		All Absent	Increased + + Thready	Decreased + + +	Such depths not required	Still Lower	
Stage 1111	None	None	Marked Pallor	Complete Paralysis		All Absent	None Elicited	Dangerous Low level + + + + +		Shock Reading	

Signs of anesthesia vary depending upon the agent used and opinions on all details are not in exact agreement. As detailed above, they represent the usually accepted phenomena seen in general anesthesia.

The *second stage* varies extremely in different individuals. In some cases especially in children, it is entirely absent, and in others its presence may be indicated merely by tremor, by the stretching of the limbs, or by irregularities in the respiration, but in the majority of cases of anesthesia it is much more marked. It often begins by movements of the arms, designed either to push away the inhalation mask or to enable the patient to rise; soon his other muscles are involved in the movement; he struggles, shouts, sings, groans, or bursts into laughter. The movements are generally not uncoördinated, but are evidently the result of some dream-like condition of the consciousness, and these dreams are often connected with the operation or with the surroundings of the patient before the inhalation began. They are, of course, determined largely by his natural mode of thought—one person prays aloud and sings hymns; another abuses the surgeon, the hospital, and all his recent surroundings, while yet another is overcome with fear of impending death and laments his unfortunate position. In this stage, the pulse is generally quickened, the blood-pressure is still elevated, the skin is flushed and often cyanotic, the respiration is extremely irregular from the struggling, and the pupil continues somewhat dilated. Vomiting may occur during this stage and is due more often to ether than to chloroform because of the former's more irritant local action. If the anesthetic be pushed, however, the movements soon become less powerful, the muscles relax and the stage of anesthesia sets in.

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While the *third stage* is divided into *four planes* in order that the anesthetist can more accurately gauge the depth of anesthesia required for different operations, a general overall summary may be made. The face assumes a calm, death-like appearance from the relaxation of the muscles, the pupils contract somewhat and may not react to light. Most reflexes disappear, one of the last to go being the closure of the eyelids on touching the cornea. The pulse and blood-pressure return to normal until plane three is reached and the same is true for respirations. The face is pale in chloroform anesthesia but may be suffused and cyanotic after ether. Plane two of this stage of anesthesia may be maintained for hours without much change, although the pulse tends to become weaker and the respiration shallower unless the greatest care be exercised, and the body temperature invariably sinks.

First plane anesthesia is marked by full, regular respiration, moderately contracted pupils, abolition of the eyelid reflex, and a ruddy color of the face. As mentioned, the pulse and blood-pressure are normal.

In the *second plane,* ocular movements are lost and the eyeball becomes fixed. Respiration, pulse, blood-pressure, and pupillary size remain essentially as in plane one. Muscular relaxation is, however, now complete.

Marked reduction in intercostal respiratory movements denotes the beginning of *third plane* anesthesia. The pupil begins to dilate and all reflexes are lost. The pulse is quickened but weaker, and the blood-pressure is temporarily elevated.

The onset of *plane four* is marked by a progressing decrease in diaphragmatic breathing and respiratory movements are very weak and shallow. The pulse is fast and thready, the blood-pressure begins to fall abruptly, and the pupils are more widely dilated. If the anesthetic is continued, respiration ceases and the pulse becomes almost imperceptible.

In the *fourth stage,* the pulse is entirely absent, all breathing has ceased, the pupil is widely dilated, and the patient is in a condition of profound shock. If death occurs, the heart completely ceases before the respiration.

When the administration of the anesthetic is stopped, the patient passes again through the excitement stage, which, however, is not generally as violent although it may be more prolonged, and then often sinks into sleep which lasts several hours. Not infrequently, however, instead of sleep, nausea, giddiness, and vomiting continue for some time after the return of consciousness.

The use of these drugs and the indications of danger in anesthesia are so important that a more detailed account of the alterations observed during their use in the human subject will be discussed in some detail.

Action.—The action of ether and chloroform on the **Central Nervous System** is similar to that of alcohol although the phenomena habitually elicited in the use of the former are very rarely produced by the latter. In all three intoxications, however, there may be observed the stages of lessened consciousness, or excitement, and of total unconsciousness. Alcohol was formerly administered in very large quantities to allow of

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surgical procedures, and its use as a general anesthetic has recently been reported. (See Alcohol, p. 266.) Furthermore, ether is also infrequently used as an intoxicant.

These anesthetics produce the same progressive paralysis of the central nervous system as alcohol, commencing with the highest cerebral functions, those of self-control, and passing downward through the lower intracranial divisions. The spinal cord is affected before the medullary centers, which are the last part of the central nervous system to become paralyzed. As in the case of alcohol, it is believed that the excitement of anesthesia is due to the suppression of self-control, and the wild movements are the result of depression with concurrent release of inhibitions. The depression of the motor areas has been shown experimentally in the case of chloroform and ether; a much stronger electric stimulus being necessary to produce movement of a limb after these drugs than before them. During the excitement stage, hyperactivity is not a sign of stimulation since the subject is usually unaware of his actions and speech. The electrical current of action disappears in surgical anesthesia and with it the conduction of nerve impulses from nerve cell to nerve cell (Forbes).

The anesthesia is not produced with equal rapidity throughout the body; the back and the extremities first becoming insensible, then the genital organs and rectum, and last of all the parts supplied by the *N. trigeminus*. The *reflexes* of the spinal cord are depressed by small quantities of ether or chloroform and are finally paralyzed completely; sometimes ether increases the reflexes for a short period. The character of the reflex is changed, for stimulation of an afferent nerve which normally causes a reflex contraction may under chloroform be followed by inhibition. A similar reversal has been described in the medulla oblongata.

Both of the anesthetics affect the *sensory* functions before the *motor* as is shown by movements occurring long after all sensation has disappeared. Later, however, the motor cells or their synapses are also paralyzed as is shown by stimulation of the cord having no effect even when the respiration is still active.

Electrical stimulation of the cerebral motor areas produces movement for some time after sensation has been lost, but as the anesthesia becomes deeper, their irritability disappears. Finally, the medullary centers are also paralyzed by the anesthetic. The medullary centers are liable to be affected by reflex stimulation up to the moment at which they cease to send out impulses for the respiratory center responds to stimulation of the superior laryngeal nerve as long as the respiration continues. It is possible that the motor cells are not directly paralyzed by the drug but can only send out impulses received from the sensory cells, and the paralysis of these is the cause of the asphyxia.

Shortly stated, the direct action of chloroform and ether on the central nervous system is a descending depression and paralysis which affects the medullary centers last of all and which involves the synapse on the sensory and receptive tracts sooner than the motor neurons.

The action of chloroform and ether on the **Respiration** is partly direct

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and partly indirect. In the first stage, the respiratory movements may be slowed or stopped temporarily by a reflex action set up by the irritation of the terminations of the fifth cranial nerve in the nose and throat and of the vagus in the larynx and bronchi, but this interruption is only of short duration and may be induced by any irritant applied to the respiratory passages (Fig. 13).

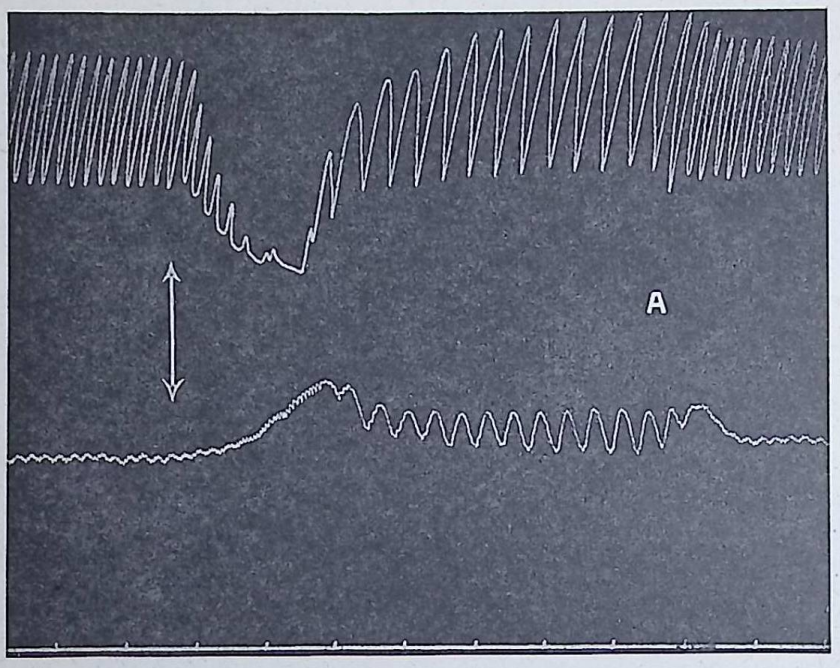

FIG. 13.—Tracings of the respiration (upper) and blood-pressure (lower) of a rabbit at the beginning of ether inhalation, which is indicated by the arrow. The respiration, immediately becomes very shallow, and then after a pause becomes slow and deep (reflex inhibition). The blood-pressure rises and the pulse is slowed by reflexes acting on the vasomotor and vagus centers. The normal condition is restored at once when the ether is removed from the nose at *A*.

Aside from the reflex stoppage of the respiration mentioned above, two types of ether apnea have been described, one coming early in anesthesia and the other quite late. The former may be seen during rapid induction of anesthesia when high concentrations of ether are used. The immediate effect is that the brain, which is richly supplied with blood, receives an undue concentration of ether which may cause cessation of breathing. The rest of the body, including the great bulk of the blood, has received no such concentration, and the cessation of the respiration having stopped further absorption for the time being, the ether in the arterial blood falls rapidly, relieving the brain of its excess, and breathing soon reëstablishes itself spontaneously. The second type of apnea is more serious as it occurs later in anesthesia when the body as a whole has absorbed a considerable amount of ether. An undue increase in ether concentration in the brain cannot be remedied so easily by the blood as in the first instance because the blood itself has a fairly high level of ether, and it may be necessary to carry out artificial respiration for a time to furnish oxygen to the blood and to aid in the elimination of the ether.

During the *second stage*, the respiration is rendered irregular by the convulsive struggling, which produces alternately periods of asphyxia and deep gasping movements. Whether or not the respiratory center is

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rendered more irritable by low concentrations of the anesthetics, it is true that ether reflexly stimulates respiration in the second stage because of its local irritating action on the mucous membranes of the respiratory passages. During planes one and two of the third stage, the respiration is regular though slightly slowed, and no reflex disturbance occurs, because the sensibility is so dulled that the continued irritation of the nerve ends causes no reflex response. As anesthesia progresses into plane three, intercostal breathing definitely decreases, and in plane four it entirely ceases, indicating a progressive paralysis of the intercostal muscles. In the fourth stage, abdominal as well as thoracic breathing ceases due to paralysis of the center—the heart continuing to beat feebly for a short time. In addition to its direct action on the center, chloroform may affect respiration in deep anesthesia by inducing anemia of the medulla through its effects on the circulation.

Since ether is very irritant locally, coughing and choking are not uncommon occurrences in the first stage. The increased mucus formation may hinder respiration and oftentimes must be removed. Furthermore, respiration may be stertorous or snoring in type since in the stage of surgical anesthesia, the tongue tends to fall back and partially obstruct breathing.

Chloroform also causes local irritation of the respiratory passages, but to a less extent than ether since it is required in more dilute concentrations. Both of these agents decrease the activity of the cilia in the trachea and bronchi (Ernst).

The effects of the anesthetics on the **Circulation** are extremely complicated because the heart varies in its reaction in different cases and under different anesthetics, and in addition the changes in the respiration and the stage of excitement add to the difficulty of the subject. The changes observed in the pulse in man have already been tabulated (p. 271). It should be stated that changes in pulse rate in the first and second stages are largely reflex in nature as a result of excitement. Later effects are due to vasomotor center depression. (See p. 273.) The blood-pressure in man has been found to be somewhat reduced by chloroform even in the earlier stages, and in deep anesthesia the fall may be very marked. Under ether, the pressure rises slightly in the first and second stages, partly from the reflexes arising from the local irritation and partly from the muscular movement. During complete anesthesia in plane three from ether, it falls to slightly above the normal or a few millimeters below it, but reaches a point indicating grave circulatory disturbance only in plane four or more especially in the fourth stage.

In animals, the first change in the blood-pressure is often a result of the slowing or even standstill of the heart from the irritation of the air passages stimulating the inhibitory center reflexly. The blood-pressure may thus fall abruptly, but in other instances the inhibition of the heart may be compensated by vasoconstriction from reflex stimulation of the vasomotor center so that the blood-pressure may rise while the heart is slowed (Fig. 14). Later, the blood-pressure falls slightly in chloroform anesthesia, but strong vapor causes a marked and dangerous fall. The heart survives after the respiration fails in most experiments, but the blood-pressure is very distinctly lower at this time (Fig. 14).

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Under ether, the blood-pressure often is slightly lower, but it remains much higher than under chloroform when the respiration fails (Fig. 15). The cause of the fall in blood-pressure under chloroform has been much disputed but is now generally ascribed to the action on the heart. Ether, being less poisonous to the heart, has a correspondingly slight action on the blood-pressure.

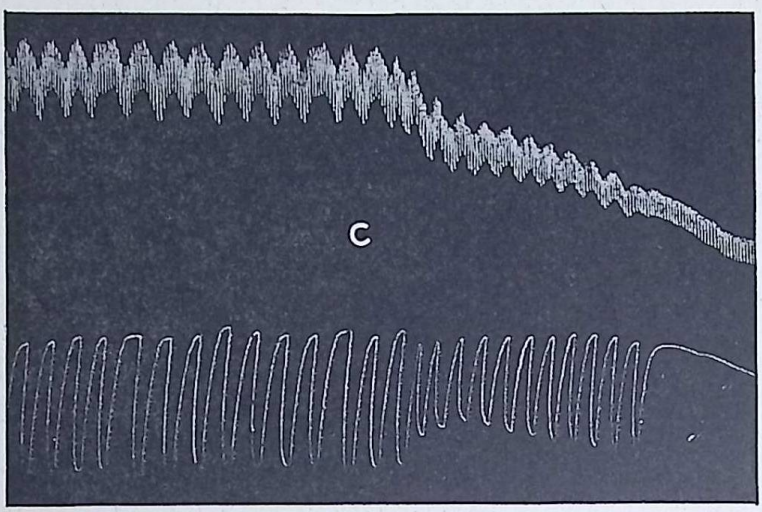

FIG. 14.—The respiration (lower tracing) and blood-pressure (upper tracing) in chloroform anesthesia in a cat. At *C* strong vapor was inhaled and a rapid fall in the blood-pressure began. The respiration ceased, the heart continuing to beat for some time. (Contrast with Fig. 15.)

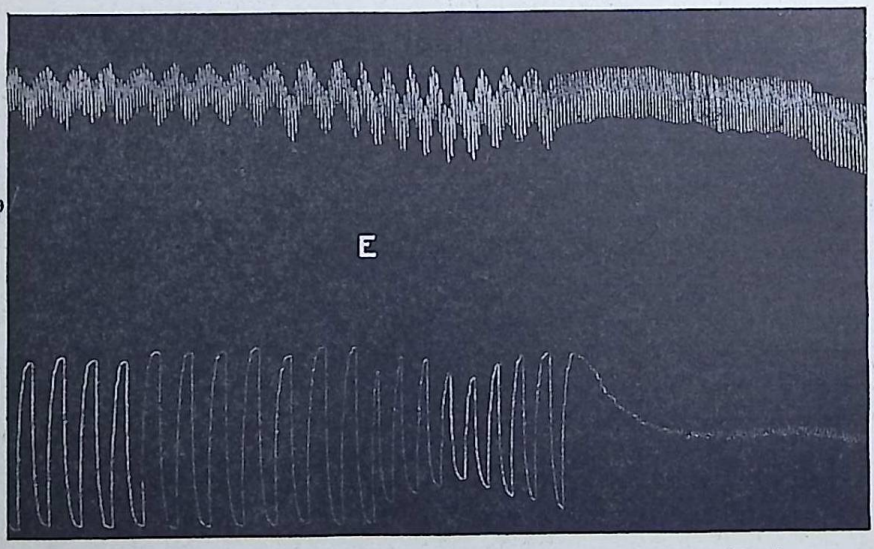

FIG. 15.—Respiration (lower tracing) and blood-pressure (upper tracing) of a cat under ether. At *E* strong vapor was inhaled and soon afterward the respiration ceased, while the blood-pressure remained high for some time afterwards. (Contrast blood-pressure in Fig. 14.)

Heart.—The frog's heart under chloroform or ether beats more slowly and more weakly and at the same time undergoes a certain amount of dilatation, all owing to the paralyzing effects of these drugs on the cardiac muscle.

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The effects on the *mammalian* heart under chloroform are very similar, but the anoxia of a falling blood-pressure is a contributory factor. The slowing is not so marked, however, as the weakness and the dilatation so that the rhythm of the pulse does not indicate the extent to which the heart is affected. The auricles are weakened by smaller quantities than are the ventricles, but the latter relax more completely in diastole (Fig. 16). The diminution in the strength of the auricles progresses rapidly while the ventricular dilatation soon reaches a maximum and is accompanied by lessened force of contraction. The auricular weakness soon becomes so great that practically no blood is expelled by its systole, and the slowing of the heart, which has not been very marked up to this point, becomes distinct. The ventricular contractions next become

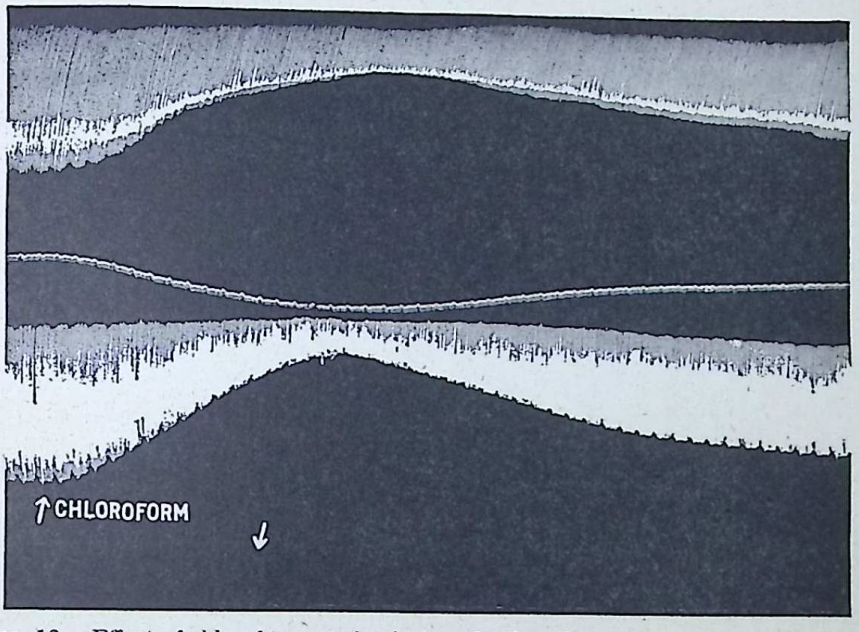

FIG. 16.—Effect of chloroform on circulation of a dog. Upper tracing, auricle. Middle tracing, blood-pressure. Lower tracing, ventricle. Levers move down in systole. Note increased dilatation and weakened systole in both cardiac chambers with fall in blood-pressure. Slow recovery after removal of chloroform. Artificial respiration.

extremely weak and occasionally fail entirely, and soon afterward the heart comes to a standstill in diastole. In its weakened state, the heart can be inhibited more easily than usual, and vagus stimulation may arrest it finally, the contractions not returning after the stimulation ceases (Embley).

When ether is inhaled in high concentrations, the changes in the heart resemble those under chloroform, but it is difficult to elicit the extreme weakness and the standstill unless asphyxia is present also.

The relative toxicity of chloroform and ether on the heart has been examined by perfusing solutions of them in Ringer's solution through the *coronary* vessels; 0.001 per cent of chloroform has a distinctly deleterious action and 0.015 was sufficient to arrest it while 0.4 per cent of ether was required to stop the heart perfused in the same way. This

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indicates that chloroform is twenty-five to thirty times as poisonous to the mammalian heart as ether; the same proportion has been found in cold-blooded animals and in mammalian hearts perfused with blood. The chloroform contained in the blood during anesthesia is sufficient to injure the heart while when ether is inhaled in a concentration leading to arrest of the respiration, it does not damage the heart muscle.

It should be remembered, however, that even during the fourth stage, arrest of respiration always precedes complete cessation of cardiac contraction. Ventricular fibrillation will be considered under the heading **Syncope.** (See below.)

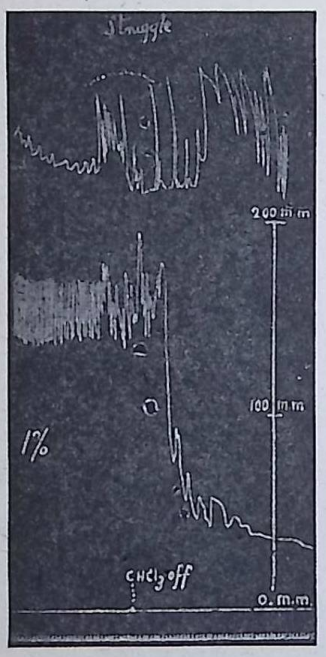

FIG. 17.—Tracing of the blood-pressure (lower) and of the respiration (upper) of a cat under chloroform; failure of the heart (ventricular fibrillation) immediately after violent struggling. The blood-pressure falls rapidly, while deep, gasping respiration continues for a short time and then ceases. (Levy.)

Vessels.—The *vasomotor center* is depressed by chloroform, and this leads to a peripheral vasodilatation. The *splanchnic vessels* are especially affected and part of the dilatation is due to a direct depressant effect on the musculature of the vessel walls. The direct action on the vessel walls may be of greater importance than that on the innervating centers. When chloroform circulates in the vessels in the concentrations used in anesthesia, it tends to relax them from a depressing effect on the muscle fibers, and dilatation from this cause may precede vessel widening due to depression of the innervating center. The low blood-pressure, however, under chloroform is mainly due to the action on the heart—in less degree to the dilatation of the vessels in the abdomen.

Ether dilates the peripheral vessels like chloroform but to a less degree when it is perfused through them, and if it is inhaled in abundance of air, this dilatation occurs in the living animal and may cause a fall in blood-pressure. This is usually absent, however, because the direct vascular action is opposed by the vasomotor center which is excited by an insufficient air supply for in ether anesthesia there is very often present a partial asphyxia induced by the close approximation of the inhaler to the mouth and nose. Late in stage three and in stage four, the vasomotor center is depressed, causing vasodilatation.

Syncope in Anesthesia.—In some experimental animals, the reaction of the circulation to chloroform is very different from the gradual depression already described. In these, the heart suddenly becomes irregular or ceases to beat abruptly, the blood-pressure falls to zero, reflexes disappear, the pupils dilate, and after a few gasping respirations, all movements cease (Fig. 17). This sudden heart failure often occurs in the early stages of anesthesia or when the inhalation is irregular or has

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been suspended. Unfortunately, such an effect may occur in the human under similar circumstances and may likewise be seen if surgical procedures are attempted before full anesthesia is reached. Early workers in this field claimed that such a response was vagal in origin, but Levy has shown that cardiac syncope during the induction period (usually the second stage) is a result of ventricular fibrillation. It is often, but not necessarily, preceded by a series of irregularities, such as extrasystoles and tachycardia. It indicates a condition of abnormal sensitization of the heart to chloroform so that the cardiac muscle becomes markedly susceptible to stimuli producing fibrillation. This form of cardiac failure is very often final, but in a small proportion of cases the heart resumes its normal contractions and the patient recovers. Inhibitory nerves may be involved in this form of heart failure, but it is very doubtful since neither vagotomy nor atropinization will correct the condition. Deep anesthesia is the best preventative for chloroform fibrillation, and this can only be accomplished by reducing the second stage as much as is practical. Fibrillation is especially liable to occur from sensory nerve stimulation during light anesthesia. Since fear and excitement increase the secretion of epinephrine in the early stages, this substance is recognized as increasing the likelihood of fibrillation, and such a relationship has been shown experimentally to be true. In other words, light chloroform anesthesia acts to reduce the refractory phase of the ventricle, thus making it more irritable so that it responds to minimal amounts of epinephrine.

Ether does not seem to have any such action on the heart, and fibrillation of the ventricle has not been observed under it. In fact, sudden circulatory failure under ether is a very rare occurrence, compared with chloroform. Henderson suggests that these rare fatalities under ether may be the result of a great reduction of the carbonic acid of the blood (acapnia), from excessive breathing during the excitement stage or during imperfect anesthesia.

Chloroform and ether hemolyze the **Red Corpuscles** and free the hemoglobin when they are shaken with defibrinated blood outside the body, but such an effect has little practical importance in actual anesthesia. Ether does appear to reduce the hemoglobin content after long periods of anesthesia, and no patient with a hemoglobin of less than 60 per cent should receive ether. Both ether and chloroform cause an increase in polymorphonuclear leucocytes during anesthesia, but the cause is not known. In he blood, chloroform is carried by the red cells for the most part, less than 10 per cent being free in the plasma. It appears to form a loose combination or solution in the cholesterol and lecithin of the corpuscles. Ether is said to be more equally distributed between the corpuscles and plasma.

According to McCollum, the corpuscles contain about 65 per cent of the chloroform in the blood—at the end of a two-hour period of anesthesia the cells containing 37 mg. and the plasma 24 mg. chloroform per 100 grams. He showed also that the brain and the other tissues store up the narcotic as the anesthesia continues so that in an hour of surgical anesthesia the chloroform content of both brain and blood is almost doubled.

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The amount of chloroform in the blood during the stage of anesthesia is about 25 to 35 mg. per 100 cc. When the respiration fails, the blood is found to contain 40 to 70 mg. per 100 cc. (Buckmaster and Gardner). During the induction of anesthesia, the arterial blood contains more than the venous, part of the chloroform being taken up by the tissues as it passes through the capillaries. On the other hand, as the anesthesia passes off, the venous blood contains more than the arterial, the anesthetic taken up from the tissues in the capillaries being eliminated by the lungs. Haggard states that in light anesthesia from ether the blood contains about 100 to 110 mg. per 100 cc., in deep anesthesia 130 to 140 mg., while 160 to 170 mg. per 100 cc. proves fatal from failure of the respiration. In addition, the relative strength of ether and chloroform is shown by a comparison of the vapor concentration of each in a hundred volumes of air required to induce various effects:

Chloroform	*Ether*	
0.5–0.7	1.5–2.5	Insufficient to cause anesthesia.
1.0	3–3.5	Causes anesthesia on prolonged inhalation.
2.0	6.0	Arrests respiration after ten to fifteen minutes.

The margin of safety in anesthesia is thus narrower than is generally recognized, for the concentration in the blood necessary for anesthesia is about half that which is fatal.

Certain **Chemical Changes** in the blood occur during anesthesia, but they are of little consequence. They may be listed as a decrease in CO_2 combining power, an increase in glucose content, an increase in urea and ammonia components, and a decrease in neutral lipoid constituents.

The behavior of the **Pupil** is of importance in anesthesia, but this sign is modified greatly by the type of preanesthetic medication employed. The combination of 15 mg. ($\frac{1}{4}$ grain) of morphine, 0.4 mg. (1/150 grain) of atropine or scopolamine, and 0.09 grams ($1\frac{1}{2}$ grain) of a barbiturate usually affect the pupil so that it tends to moderately constrict. Hence it reacts similarly as shown in the table on page 271. During the first and second stages, it is generally somewhat dilated due to the excitement which induces increased sympathetic activity—even though preanesthetic drugs have been administered. During the recovery stage, it is also usually dilated due to reflex excitement. As soon as complete unconsciousness is attained, it becomes rather narrower than it is normally, not only because of preanesthetic medication but because sympathetic tonus is decreased. In the latter half of plane three, dilatation occurs again and becomes marked in plane four and in the stage of medullary paralysis. Such an effect is explained on the basis of relaxation of the constrictor muscles plus the depressant effect of increased carbon dioxide. As the patient recovers, the slight dilatation slowly recurs; if the respiration and circulation be dangerously weak, rapid dilatation occurs in most cases. Dilatation of the pupil in the stage of anesthesia, therefore, indicates danger unless it is accompanied by symptoms of returning consciousness, such as reflex movements and vomiting.

The local effect of the anesthetics on the **Alimentary Canal** are chiefly confined to irritation with resultant reflexes although other actions do

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occur. The *vomiting* which is so often a feature of anesthesia may arise in part from the irritating action on the stomach of the chloroform or ether swallowed in the mucus but is mainly of central origin, for vomiting also occurs when ether is injected intravenously in man and also under nitrous oxide anesthesia in some cases; here the local irritation can only play a small part, and the medullary center is probably involved directly, perhaps in the same way as occurs in shock and collapse. In the early stage, vomiting sometimes occurs from the odor and taste of the anesthetic, more especially in people who have been anesthetized previously and have unpleasant associations with the odor.

The ordinary movements of the stomach and intestine have generally been supposed not to be influenced by the anesthetics, but Miller has shown that in dogs both ether and chloroform administrations are followed by marked relaxation of stomach, small intestine, and colon. Sleeth and Van Liere found that chloroform delays the emptying time of the stomach by 60 per cent, ether by 40 per cent, nitrous oxide and ethylene by 15 per cent, cyclopropane and divinyl ether by 7 per cent. The diminution in the movements of the various parts of the alimentary canal makes its appearance immediately following the irregularities, occurring in the excitement stage and may be produced, in part at least, by temporary asphyxia due to the struggling. During the stage of surgical anesthesia, there is complete inhibition of the smaller contractions of the muscular structures, or peristalsis, and also loss of muscular tone, and this effect is due to sympathetic stimulation. As recovery from anesthesia follows, there is a gradual return to the normal conditions although complete recovery may not take place for some hours. The stomach frequently remains somewhat depressed for hours while the small intestine may be abnormally active, and the colon shows a high degree of tonicity.

These alterations in the activity of the alimentary canal are produced by the action of the anesthetics upon the canal itself, the central nervous system apparently not being involved. It is quite probable that the changes described are responsible for some of the unpleasant postoperative symptoms sometimes encountered. The relaxation of the stomach will favor gastric dilatation and vomiting, the exaggerated intestinal peristalsis may be responsible for the "gas pains" and the spastic condition of the colon will favor accumulation of gas and fluid above the point of contraction.

The **Kidney** appears to be affected in a certain proportion of cases of anesthesia in man as is shown by the appearance of albumin in the urine. Chloroform induces typical fatty degeneration occasionally while albuminuria has been observed in a certain proportion of cases after ether. The proportion of cases in which this organ is affected seems to vary extraordinarily. However, chloroform is considered more deleterious to the kidney than is ether. Both agents cause albuminuria of as much as 5 to 40 per cent, and phosphates are always markedly increased. The secretion of urine is generally diminished during anesthesia with chloroform or ether due to the reduced blood-pressure and imperfect aeration of the blood. MacNider finds that in the dog the

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damage to the kidney from the anesthetics is much greater in old animals than in young ones and brings this into relation with the amount of stainable lipid in the renal cells. After recovery from ether anesthesia some diuresis may occur, or the urine may remain scanty for some hours.

The **Uterine Contractions** during parturition seem little influenced by moderate anesthesia but are somewhat slowed in the deeper stages. Chloroform and ether pass into the fetal blood, and some experiments are recorded in which the fetus was killed by the inhalation while the mother recovered. This may be caused either by the direct action of the drug on the young animal or by the low maternal blood-pressure leading to its asphyxia. It does not seem dangerous to induce a moderate degree of anesthesia during labor in human beings (the analgesic stage only is required unless special procedures are necessary) although here, too, the effects on the child are shown by an increase in the nitrogen excretion in the urine for some days.

The **Temperature** falls during anesthesia of even short duration. During forty-five minutes of complete anesthesia with chloroform, it may be reduced as much as 1.5 to 2° C. This action is due partly to the greater output of heat through the dilated skin vessels but mainly to the lessened heat production from the diminished muscular movement and to a depression of the heat regulating center. The production of CO_2 also falls and doubtless the oxygen absorption. This is not evidence of direct action on the tissues but is one of the consequences of the central nervous depression.

Much has been written regarding the effects of the anesthetics on the **Metabolism of the Tissues.** It is now generally recognized that chloroform, in addition to its action on the central nervous system, produces marked changes in the nutritive processes of protoplasm. The simpler organisms, which are devoid of nervous structure, are killed in comparatively dilute solutions, and chloroform water, therefore, retards putrefaction, the fermentation of yeasts, and the movements of cilia. In the higher animals and in man, the processes of life and nutrition of the different organs also undergo alteration, quite apart from the effects on the nervous system. Thus fatty infiltration of various organs is produced by chloroform administered repeatedly and even by a single inhalation in some cases. The organs especially implicated in this change are the liver, heart, and kidneys, but degeneration of ordinary muscle has also been observed occasionally. Experimentally, such an effect is enhanced if a high fat diet is given simultaneously. (See Hepatotoxic Effect, p. 261.)

Further evidence that, even in ordinary anesthesia, the damage to the liver from chloroform used as an anesthetic is by no means negligible is shown by the experiments of Rosenthal and Bourne. These workers found that normal dogs excrete in the bile within fifteen minutes at least 85 per cent bromsulphthalein which has been given intravenously. On the other hand, if the liver has been damaged, the removal of the dye is greatly delayed. When the animal was subjected to chloroform for even half an hour, dye retention lasted for eight days, and when chloroform was given for two hours, dye retention lasted for six weeks.

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With ether, however, while there is some evidence of damage as is shown by a slight delay in the excretion of the dye, the damage is evidently quickly repaired as excretion is normal on the second day. Ravdin and his co-workers have found that 35 per cent of the glycogen is lost from the liver during two hours' anesthesia with chloroform and 94 per cent during the twenty-four hours following anesthesia. As the liver glycogen decreases, the fatty acid concentration in the liver increases, effects due to an action on the liver parenchyma.

The effects of chloroform on the nutrition of the tissues are shown in the urine secreted during and after anesthesia. The nitrogen eliminated is constantly increased, and the unoxidized sulfur shows a similar augmentation, and these would seem to indicate an increased protein destruction and a disturbance of the oxidation in the tissues.

The carbohydrate metabolism is also impaired for acetone and sugar are often present in the urine after chloroform, and it has long been known that diabetes is liable to be aggravated by this anesthetic and may prove fatal. The sugar of the blood is increased, and the glycogen of the liver diminished or absent, from a specific action on the liver cells.

Bile pigment is said to occur in the urine in a considerable number of cases of anesthesia with chloroform, especially one or two days after the administration. The chlorides and the acidity of the urine are also augmented.

These effects of chloroform on the metabolism resemble very closely those of phosphorus poisoning. They seem to occur only after those substances of the aliphatic series in which chlorine is substituted, ether having little or no effect in producing fatty degeneration or in changing the proportion of the sulfur compounds in the urine. An excess of sugar is found in the blood after ether anesthesia in dogs and leads to glycosuria. It was suggested that this might arise from excessive activity of the suprarenal bodies during the excitement or during partial asphyxia and not from any direct action of the ether on the metabolism, but this is not correct as the condition is also found in animals from which the suprarenal glands have been removed. In light anesthesia from ether, the available alkali of the blood is slightly reduced, and the hydrogen-ion concentration rises, and this becomes more marked as the anesthesia becomes deeper. This condition of acidosis is probably largely due to the production of lactic acid which seems to come from the muscles.

The **Excretion** of both ether and chloroform takes place mainly by the lungs. Most of the anesthetic is eliminated very rapidly (blood levels being reduced 50 per cent, five to seven minutes after the anesthetic is removed), but traces of chloroform are said to be found in the breath for twenty-four hours after the inhalation and even longer in cases in which there is a tenacious mucous secretion in the bronchi. With ether, however, none is detectable after four hours. Small quantities of chloroform escape by other channels for it has been found in the urine and is said to occur in the perspiration and the milk. Ether is eliminated almost exclusively by the lungs as approximately 90 per cent of the amount absorbed has been recovered from the expired air after cessation

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of the administration. Small amounts are excreted in the urine where the ether concentration approximates that in the arterial blood. This is due to the fact that, like the brain, the kidney blood supply is abundant, and there is little difference in the ether concentration between the arterial and venous blood in this organ. Nevertheless, the amount of ether so eliminated in the urine is slight due to the small amount of urine excreted during anesthesia. Small amounts of ether are also eliminated in the sweat and also by the serous surfaces as is shown by the fact that air enclosed in the abdomen during anesthesia rapidly assumes a partial pressure of ether equal to that of the alveolar air. The rate of excretion of both agents can be markedly increased by administration of carbon dioxide, a procedure useful in anesthetic practice.

Comparison of Ether and Chloroform.—The depressant effect of chloroform on the brain is thus 3 to 3½ times as great as that of ether, and its power to arrest respiration is about 3 times as great. The depressant action on the heart of chloroform is about 25 to 30 times that of ether, and the extremely dangerous cardiac syncope which may be seen under chloroform is unknown under ether. Ether has to be given in more concentrated form to produce anesthesia and therefore produces more irritation of the air passages as shown by the greater secretion of saliva and mucus, by coughing, and by the sensation of asphyxia. Anesthesia is produced with greater difficulty and more slowly than with chloroform, and the stage of excitement is generally more violent and prolonged. But the pulse is not nearly so much affected as by chloroform; it may be somewhat slower than usual but is full and strong. The concentration of chloroform which is necessary to produce anesthesia is very close to the concentration which causes serious impairment of the heart's action while, on the other hand, 3½ per cent ether vapor is sufficient to maintain narcosis, but a very much stronger concentration is required to cause a dangerous condition of the heart (p. 277). In the same way, the difference in the concentration required to produce anesthesia and that which will stop the respiration is smaller in chloroform than in ether, and the anesthetist has thus more leeway when the latter is used. The changes in the metabolism following the use of chloroform are not produced to the same extent by ether.

Regarding the **Choice of an Anesthetic,** ether is less liable to cause dangerous symptoms than chloroform and ought, therefore, to be used instead of chloroform wherever feasible. Ether is contraindicated in acidosis, acute respiratory disease, pulmonary tuberculosis, and increased intracranial pressure. Given expertly, much of the objection to its irritant action may be overcome. Chloroform is preferred by the patient for it causes less irritation and less feeling of suffocation, and it may be preferred by the surgeon because it induces anesthesia sooner and less of it is required. However, the inherent toxicity of this agent and the too often improper administration of it are reasons why it is now rarely used. Chloroform is definitely contraindicated in renal and hepatic disease, in heart disease, and in the aged. In drunkards, ether sometimes fails to induce deep anesthesia, and in very hot climates anesthesia with ether may be difficult and unpleasant to induce owing

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to its rapid evaporation. Lastly, where artificial lights are necessary (except the electric) or where the actual cautery is to be used, ether is dangerous on account of its inflammability, and chloroform would be preferred if other anesthetics were not available.

The **Dangers of Anesthesia** are caused only in part by the direct action of the ether or chloroform. The important thing to remember is that directly or indirectly, most anesthetic complications are the result of interference in the maintenance of a proper supply of oxygen to the tissues along with a failure to adequately remove carbon dioxide. Fatal accidents have occurred from objects such as false teeth or tobacco plugs falling into the air passages and causing asphyxia while vomited matter has been drawn into the larynx in some cases. Such causes of death may, as a rule, be entirely prevented if the patient has been properly prepared. Very often the relaxation of its muscles permits the tongue to fall back into the throat, rendering the breathing labored and stertorous; this is at once relieved when the tongue is drawn forward. The accumulation of saliva and mucus or blood in the throat may lead to similar symptoms. In these accidents, the chloroform or ether is only indirectly the cause, but in a large and ever-increasing number of cases, the fatal effects must be ascribed to the direct action of the anesthetics. The proportion of accidents during anesthesia is very difficult to estimate, and there are great discrepancies in the statistics of different surgeons. A fair average would seem to be 1 death in 4,000 chloroform inhalations with a range of from 1 in 3,500 to 1 in 15,000. The statistics of ether fatalities also vary from 1 death in 3,000 to 1 in, 16,000 cases, but probably 1 in 10,000 to 12,000 cases would represent the average mortality.

The **Cause of Death** in anesthesia due directly to the agents used has been a subject of discussion for over fifty years. Today, cardiac syncope (ventricular fibrillation), overdosage, and explosions are considered most important. The first cause, seen only with chloroform has already been discussed (**Syncope**, p. 278). Suffice it to repeat that it may often be prevented if the anesthetist passes the second stage quickly and maintains full surgical anesthesia.

A second form of accident in anesthesia may be from *overdosage* and is less likely to be fatal. In this form the respiration becomes shallower and finally ceases while the pulse can still be felt or the heart beat can still be heard. The interval between the failure of the breathing and that of the pulse varies in different accounts, and in some both are said to have disappeared simultaneously. But in these cases the gasping respiration, which is characteristic of the cardiac syncope, is not seen. This accident occurs especially when the anesthetic has been pushed or after prolonged inhalation. It may occur under chloroform or ether, and the majority of fatalities under the latter appear to be of this character while the great bulk of chloroform deaths are due to cardiac syncope. This death from overdosage is easily elicited in animals and has been the subject of a large amount of experimental investigation, which has been directed chiefly to the question whether the respiration or the heart is the first to fail. When concentrated vapor of ether or

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chloroform is administered, the heart still beats after respiration stops. However, chances of resuscitation are negligible if the agent has been chloroform since its marked depressant effect on the myocardium precludes much hope of recovery. From a practical point of view, it is of comparatively little importance whether there are a few fluttering beats of the heart after the last inspiration or not. The all-important question is whether the heart has been so injured as to be unable to carry on the circulation. Ether does not possess this untoward effect of chloroform and hence artificial respiration will usually restore normal air exchange and complete recovery.

It has been suggested that stoppage of respiration is due in part to anemia of the brain caused by a falling blood-pressure. This is difficult of proof, and the direct depressant effect on the respiratory center is sufficient explanation. With ordinary care, respiratory arrest due to overdosage is unnecessary. If the anesthetist avoids hyperpnea, oxygen deprivation, or excessive concentrations of anesthetic agents, this cause of death will cease to exist.

A third cause of death deserves brief mention. Ether has caused more explosions than any other inflammable anesthetic since there have been more ether anesthesias. Fatalities depend upon the flame gaining access into the lungs, and they may be ruptured if the explosion is violent enough. Until oxygen was used with ether, such accidents did not occur and ordinary precautions regarding open flames and cautery will prevent deaths due to ether explosions.

The autopsy in cases of death by chloroform or ether shows no specific lesions. The blood is often dark colored from the asphyxia, and the heart is found dilated. Irritation of the respiratory passages may be present in ether poisoning, and the odor of the anesthetic may be recognized in the different organs. Microscopic examination may show some alterations in the cells of the respiratory center and cardiac ganglia, fragmentation of the heart muscle, and some parenchymal degeneration of the liver, kidneys, spleen, and heart after chloroform.

Late Deaths.—In the past, many postoperative deaths were attributed to chloroform and ether. It is recognized today that most of them either could have been prevented or were due to some other factor. If chloroform is never administered in the presence of renal, hepatic, or cardiac disease, and if liver glycogen is maintained at high level prior to its use, "delayed chloroform poisoning" due to parenchymatous damage of the liver will rarely occur. In the same manner, postoperative pulmonary deaths due to ether need not occur if the patient is kept warm during the anesthesia and if the anesthetist is well-trained in its administration.

Ether Convulsions.—The etiology of violent involuntary muscular contractions during ether anesthesia still remains obscure. Clonic movements of the limbs may, as has already been described, occur early in ether anesthesia and usually pass off when anesthesia is deeper. Apart from the inconvenience they cause, these convulsive movements are of little importance. Occasionally convulsions occur later in the anesthesia which are of much more serious import. They are often preceded by irregular and rapid respiration followed by twitching in the muscles

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of the face. The convulsions may spread quickly to other muscles, rendering it difficult to keep the patient on the operating table. It is a grave condition as the convulsions may persist until the patient dies. Payne concludes that the late ether convulsions are due to a combination of factors; extreme youth of the patient, toxemia, deep anesthesia, and high external temperature. While the mortality has been previously stated to be 18.9 per cent, Papper recently reported 6 cases, all of whom recovered. The most satisfactory treatment was chloroform and intravenous sodium pentothal.

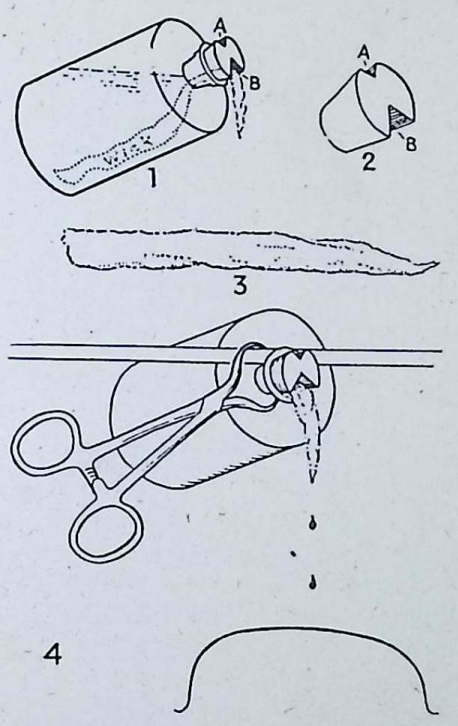

FIG. 18.—*1*, The container of the anesthetic liquid; *2*, the cork with two notches—one small (*A*) and one large (*B*); *3*, the wick—a strip of gauze or cotton long enough to reach to the bottom of the container, and coming to a fine point at the outer end; *4*, arrangement for convenience in maintaining a constant drip—the dripper may be fixed above the mask to a gooseneck support or to a screen by means of a bull's horn forceps. (From "Fundamentals of Anesthesia," courtesy of American Medical Association Press.)

Apparatus and Principles.—A detailed account of the apparatus used in anesthesia and the techniques of administration do not properly belong in a text of pharmacology. Such information must be learned from practical experience in the hospital. Flagg puts it best when he says, "The administration of anesthesia is much more than the application of mere laboratory technique which may be set forth and employed under controlled conditions. It is one of the most critical branches of therapeutics." For details of various methods of administering anesthetics such as endotracheal, intratracheal, and intrapharyngeal inhalation; for insufflation techniques and others, the reader is referred to Flagg's excellent book, *The Art of Anesthesia.*

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The "open" drop method for administering ether and chloroform remains popular because of simplicity and controllability (Figs. 18 to 20). However, the technique must be as carefully learned as though ether were being administered by means of the more complicated gas machine, a method now preferred in many hospitals.

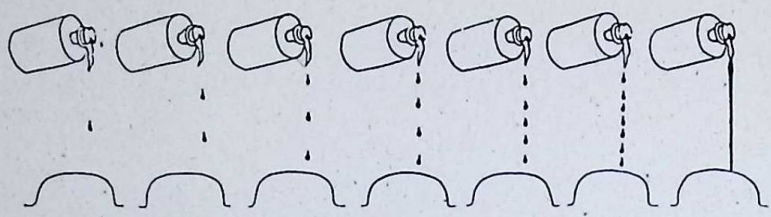

FIG. 19.—During induction the drip should be accelerated slowly, steadily and as rapidly as the patient will tolerate, never exceeding the amount that will vaporize on the mask. Throughout the administration the drip should be continuous—the rate varying as changes in depth of anesthesia are required. (From "Fundamentals of Anesthesia," courtesy of American Medical Association Press.)

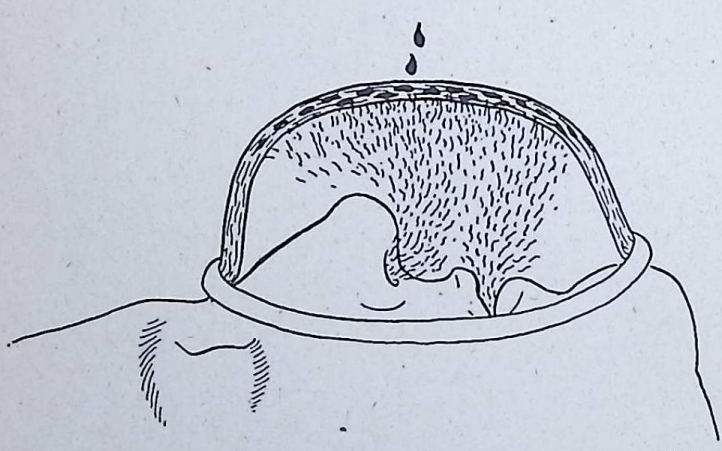

FIG. 20.—The vapor concentration depends on: (*a*) the temperature and the barometric pressure; (*b*) the rate of flow of air through the gauze, *i. e.*, the minute volume of respiration; (*c*) the amount of agent on the gauze, and (*d*) the volatility of the agent. The vapor of all volatile agents is heavier than air and falls downward. (From "Fundamentals of Anesthesia," courtesy of American Medical Association Press.)

The chief principle to be kept in mind is that at all times an adequate airway must be maintained so that the tissues never lack ample oxygen or suffer from an excess of carbon dioxide. Finally, the good anesthetist observes the patient as a whole, not just the head.

Preliminary Examination.—Before anesthesia, a careful examination should be made of the condition of the patient, and if there is great anxiety and excitement, a hypodermic injection of morphine and atropine and/or one of the barbituric acid group of drugs may be given. (See **Preoperative Premedication**, p. 307.) Valvular disease of the heart does not contraindicate an anesthetic unless there are marked symptoms of inefficiency, such as dropsy or edema. Administration of ether or chloroform to a patient with atheromatous arteries is dangerous due to the tendency of producing apoplexy during the second stage, and if a

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general anesthetic seems absolutely necessary, an opiate must always be given previously. In cases of bronchitis and catarrh of the air passages, chloroform or the gas anesthetics are to be preferred to ether as they are less irritating while in Bright's disease chloroform is generally more injurious than ether due to the resultant albuminuria and tendency to fatty degeneration. Here again the gas anesthetics are to be preferred. Where there are symptoms of anemia and the hemoglobin is found to be deficient, great care is necessary in the use of ether and chloroform.

Practical Anesthesia.—The patient preferably should not have anything to eat for several hours before the anesthetic is to be given so that the stomach may be empty and vomiting avoided as far as possible. False teeth and any other foreign objects must be removed from the mouth. A loose hospital gown should be worn, and in addition, blankets should be used to keep the patient from chilling. The eyes are closed in order to protect the conjunctiva from the irritating vapor, and vaseline is applied to the eyelids, lips, and nose to further reduce irritation. When the "open drop" method is used, it is essential that the mask be freely permeable by the air and not fit closely to the face. It must be remembered that the air passes through cloth with much greater difficulty when it is wet by the saliva and mucus and that a mask which is freely permeable at the commencement of an operation may lead to asphyxia after it has been soaked during the first and second stages. The patient is instructed to breathe as regularly as possible or to count from one upwards, and some of the anesthetic is dropped on the mask (Fig. 18). If the breath be held, the mask should be raised a little from the face as the next inspiration will be a very deep one. During the excitement stage, the respiration is irregular, and great care must be taken to avoid the inhalation of too concentrated vapor. As soon as the conjunctival reflex disappears, the mask is raised and is replaced when it reappears. The anesthetist should maintain an even anesthesia and avoid sudden changes. Throughout the anesthesia, care must be taken to prevent any interference with the respiration by the operator leaning on the thorax or abdomen. Very often stertorous respiration sets in from the tongue falling back into the throat, and this has to be remedied by pressing forward the angle of the jaw or if this is not sufficient, by pulling out the tongue with a blunt-pointed forceps. Vomiting is a very common occurrence in ether anesthesia, especially during the early stages, and when it sets in, the head is turned to one side and the vomited matter removed with a sponge. The anesthetist should watch for impediment of respiration by mucus and be ready to aspirate it when necessary.

At all times, the anesthetist should concern himself chiefly with respiration, the color, muscular tone, the size of the pupil and eye reflexes, and the pulse. The first two are of greatest importance during the first and second stages of anesthesia. The last three assume importance as surgical anesthesia is reached and maintained since they assure the anesthetist of the condition of his patient. A reflex arrest of respiration often occurs in the first stage but is not of importance in itself but only from the deep gasping inspiration which follows it. Serious accidents during anesthesia have already been discussed, but when respiration fails because the anesthetic agent is used in a too concentrated form, immediate attention becomes necessary. The head ought to be lowered at once, and the lower limbs elevated in order to drive the blood to the head as far as possible and thus remedy the anemia of the brain from the weakness of the heart that accompanies the cessation of the respiration. The epiglottis must be raised by pressing forward the angle of the jaw or by pulling forward the base of the tongue. Artificial respiration in one or other form ought to be commenced at once and carried on as long as is necessary; a large number of methods of performing artificial respiration have been proposed, but they can only be taught in practical class and need not be entered upon here. If the pulse is weak, intermittent pressure over the heart may aid it in carrying on the circulation, and in some cases the abdominal cavity has been rapidly opened and the heart compressed between one hand below the diaphragm and the other on the

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chest wall. This heroic measure has in some cases restored the heart beat and the respiration. Various drugs have been recommended in these cases, but it is exceedingly questionable whether they are really of service. Caffeine, nikethamide (coramine), and metrazol (cardiazol) are most commonly tried as respiratory stimulants. In animal experiments, the best results in circulatory failure are obtained by the intravenous or intracardiac injection of epinephrine in saline solution, and this method has proved successful in man.

The ventricular fibrillation caused by chloroform is usually always fatal. Care in administration of this agent during the second stage will prevent most cases. When it does occur, epinephrine must not be used since the condition is only made worse. In addition, the operation should never be commenced until anesthesia is complete; otherwise, reflex inhibition of the heart leading to fibrillation may result and lead to fatal consequences.

In long operations, the attention of the anesthetist should be directed to maintaining an even level of unconsciousness. When anesthesia is reached, it may be maintained by comparatively small quantities, and on the other hand, owing to the fall of temperature and the prolonged action of the drug, the amount necessary to produce cessation of the respiration and the heart is much smaller than during shorter operations.

On the completion of the operation, the patient should be watched until there is complete recovery of consciousness. After prolonged anesthesia, the patient should be kept warm as the temperature often continues to fall for some time after the administration of the drug has ceased. If vomiting persists after the recovery of consciousness, cracked ice may be given, and relief is sometimes obtained by lavage of the stomach.

The patient should always be placed in the recumbent position when possible as otherwise anemia of the brain and fainting are liable to result.

Therapeutic Uses.—Anesthesia is generally induced for the purpose of surgical operations and examinations and in labor. Not too many years ago when it was necessary to perform an operation or manipulation involving much pain, the surgeon had to consider only which of the two general anesthetics was the better adapted to the case. The improvements introduced in the methods of inducing local anesthesia and the introduction of new and effective drugs as surgical anesthetics have now enlarged his field of choice, and the further question has to be met whether unconsciousness is desirable, or whether the necessities of the case may not be met by paralyzing sensation at the site of operation only. The advantages claimed for local anesthesia will be discussed later, but the general conditions in which chloroform and ether are to be preferred may be stated shortly. General anesthesia is absolutely essential where complete relaxation of the muscles is desired and where the movements of the patient may imperil the success of the operation. Ether administered by various techniques is still the anesthetic of choice by many anesthetists and surgeons. Its local irritating properties on respiratory passages and its tendency to cause vomiting are of little significance compared to its relative safety. Operations on the abdominal organs and around joints and such others as involve wide and deep incisions are best performed under ether. Chloroform on the other hand is rapidly being discontinued as a general anesthetic because of its potential toxic effects.

For symptomatic relief in cases of extreme excitability of the central nervous system, as in strychnine poisoning, tetanus, and other convulsive affections, a few whiffs of chloroform or ether are generally

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sufficient to produce quiet, often without affecting the consciousness to any marked extent. In cases of very acute pain, chloroform or ether have been used, but as a general rule morphine or opium is preferable.

Ether in combination with hyperimmune serum has been used in the treatment of experimental western equine encephalomyelitis of mice (Sulkin, *et al.*).

The **Local Action** of chloroform and ether on the stomach and skin is entirely independent of their action as anesthetics and is discussed separately below. Chloroform has a hot, sweetish taste while ether is bitter and suffocating in the mouth; a sensation of heat and often of pain in the stomach follows when they are swallowed, and chloroform may cause gastric irritation and catarrh when given undiluted. When ether has been exposed to air and sunlight and to a varying temperature, it may contain acetaldehyde and peroxide bodies, which render it more irritant to the mucous membranes. The whole effect is similar to that produced by the volatile oils, but absorption probably takes place more rapidly. On the skin, ether evaporates too rapidly to cause much irritation, but chloroform is occasionally used as a rubefacient in the form of a liniment.

These preparations are used for the same purposes as the corresponding preparations of the volatile oils. Thus the spirits may be prescribed as carminatives or in colic, while the liniment is used as a counterirritant. Chloroform water is an antiseptic of considerable power but is too volatile for surgical use.

Hoffmann's drops is a favorite carminative and is often added to other drugs to lend them an agreeable odor and taste. This preparation is also used in dilution as a stimulant in the same indefinite way as wine and spirits, and its large percentage of alcohol entitles it to be ranked among the alcoholic preparations.

Spirits of ether is used occasionally in expectorant mixtures and is believed to increase the bronchial secretion.

Ethyl Chloride (C_2H_5Cl) was discovered by Florens in 1847. It is a volatile liquid with a not unpleasant ethereal odor. It should be emphasized that it is explosive as well as inflammable.

It is used as a local anesthetic inducing its local action by freezing. When sprayed in a fine jet under pressure, the evaporation of this liquid is extremely rapid. The temperature of the skin surface is brought below freezing and this process acts as a terminal anesthetic. Effects are complete in a few seconds and last long enough to permit, for example, the lancing of a boil. It does not compare with the procaine group of local anesthetics in efficiency but is useful because of the simplicity of its administration.

Because of its toxicity and narrow margin of safety, it is not used as a general anesthetic. The rate of induction is more rapid and pleasant than with ether or chloroform as is the rate of recovery, but muscular relaxation is not complete. Its effects on the heart are similar to chloroform while those on respiration resemble ether. The amount necessary to produce anesthesia varies greatly, and because of this, it is difficult to maintain a constant state of unconsciousness.

Ethyl chloride is obtained by the action of hydrochloric acid on alcohol and is a gas at ordinary temperatures but is supplied condensed into a colorless

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fluid. It is very volatile, inflammable and mobile, and is liable to contain traces of the same impurities as have been mentioned under chloroform. It should be kept in a cool place away from lights or fire.

Divinyl Ether.—Divinyl ether (vinyl ether or divinyl oxide, Vinethene (N.N.R.), $CH_2:CH.O.CH:CH_2$) is a clear, colorless liquid which boils at 28.3° C. and is highly inflammable. Leake and Chen first suggested its use in 1930. It has been introduced as a volatile anesthetic, and at the present time it is used only for short operations, in obstetrics, in dentistry, and as an induction anesthetic. It may be given by the closed or by the open method, but in any event it is of paramount importance to maintain an adequate air supply and an unobstructed airway.

It differs from ether chiefly in its rapidity of action, and this effect not only makes it more toxic but makes maintenance of surgical anesthesia more difficult. Anesthesia comes on quite rapidly under its influence, usually in from one-half to one and one-half minutes, and recovery is in like manner rapid, occurring in about two and one-half minutes. In addition, it is less irritant to the respiratory tract than ether, and it produces little or no postoperative nausea. It produces good, but not complete, muscular relaxation and is superior to ethyl chloride in not producing spasm of the respiratory muscles.

It is difficult to recognize the usual signs of anesthesia when divinyl ether is used. Eye changes are entirely unreliable, and the anesthetist must depend largely upon the rate, depth, regularity, and character of the respiration. As a rule, respiratory movements are somewhat increased at first and then return to normal with complete anesthesia. With an adequate airway, the color is good and the blood-pressure and heart are usually unaffected. Overdosage causes respiratory arrest with resultant anoxemia and cyanosis. This may occur frequently unless the anesthetist carefully watches the patient, but it can be corrected by stopping the anesthetic and administering oxygen.

The concentration of vinyl ether in the blood is considerably below that of ethyl ether when equal degrees of narcosis are compared. For instance, in the third stage of anesthesia a concentration of 18 mg. per 100 cc. is as effective as compared with 132 mg. per 100 cc. of ethyl ether. This figure would not necessarily indicate a greater degree of safety but might merely indicate a more potent agent. In experimental animals under artificial respiration, divinyl ether at a level 30 to 40 per cent above that needed to cause respiratory arrest was more prone to cause alterations in heart rhythm than ether and cyclopropane. However, under similar circumstances, blood-pressure was not maintained with divinyl ether or diethyl ether as well as with cyclopropane.

A few deaths have been reported following its use, and the effect of the substance upon the liver seems to be of especial importance, which would indicate that caution should be used in employing it in long operations or in those in which there is any suggestion of previous hepatic impairment. For this reason, it has been recommended that it should not be employed for longer than one-half hour when it is given by the open method although it may questionably be given for a longer time when used with oxygen in a closed system.

Used judiciously in short operations, divinyl ether is a suitable

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addition to the anesthetist's armamentarium. It seems particularly useful in nose and throat operations since it produces little if any coughing. While useful in obstetrics, its great rapidity of action makes it difficult to obtain simple analgesia.

Because of its potential toxic effects, it is contraindicated in renal, hepatic, and cardiovascular disease. It deteriorates very rapidly when exposed to air and should never be used longer than twenty-four hours after a container of it has been opened.

Trichloroethylene.—(U.S.P.) While not now used as a general anesthetic to perform operations, this agent is nevertheless capable of producing anesthesia and hence is mentioned here.

Trichloroethylene is a chlorine derivative ($CHCl:CCl_2$), occurring as a colorless liquid with a pleasant, sweetish odor. Originally used as a solvent in industry, it was noted that workers often lost sensation of the area supplied by the fifth cranial nerve. Jackson introduced it as a general anesthetic in 1934, but it never became popular. It has also been recommended in trigeminal neuralgia (tic douloureux), angina pectoris, and migraine.

In spite of the supposed selective action of trichloroethylene on the sensory nerve endings of the fifth cranial nerve, recent evidence indicates that the relief obtained in this condition must be due to its central depressant effect.

Acetylene ($HC{\equiv}HC$) has been used as a general anesthetic with good results but because of its explosiveness has not become popular. It results in no unpleasant after effects but must be used in high concentration (about 70 volumes per cent) to produce anesthesia. It was introduced by Grollman for the measurement of the cardiac output in the human and has replaced other gases formerly used for this purpose.

Various other members of the aliphatic series have been introduced as general anesthetics at various times, but they have all been found to be too toxic for general use. Among those may be mentioned *trimethylethylene* (pental), *ethyl bromide*, and *ethylene dibromide*.

Of more recent interest is **cyprethylene** introduced by Krantz and his collaborators. This compound possesses a high anesthetic potency, produces good muscular relaxation, and may be administered in a mixture with high oxygen content.

Preparations

Æther, ether, ethyl ether, diethyl ether ($C_2H_5.O.C_2H_5$) (U. S. P.), contains from 96 to 98 per cent of $(C_2H_5)_2O$, the remainder consisting of alcohol and water. It dissolves in about 12 volumes of water and is miscible with alcohol. *Caution*—Ether to be used for anesthesia must be preserved in tight containers of not more than 3 kg. capacity and is not to be used for anesthesia if it has been removed from the original container longer than twenty-four hours.

Æther, ether $(C_2H_5)_2O$, (B. P.), is ethyl ether obtained by distilling a mixture of ethyl alcohol and sulfuric acid. It is soluble in 8.5 volumes of water and miscible with alcohol. Dose, 1 to 4 mil.

Ether is a transparent, mobile liquid, with a characteristic odor and a burning taste. It is highly volatile and inflammable.

Æther Anæstheticus, anesthetic ether (B. P.), possessing the characters of ether.

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ÆTHYLIS CHLORIDUM, ethyl chloride ($CH_3.CH_2Cl$) (U. S. P.), (C_2H_5Cl) (B. P.), slightly soluble in water and freely soluble in ether.

Ethyl chloride vapor is very inflammable and is a colorless, mobile, very volatile liquid.

ÆTHYLIS OXIDUM, ethyl oxide ($C_2H_5.O.C_2H_5$) (U. S. P.), contains 96 to 98 per cent of $(C_2H_5)_2O$, the remainder consisting of alcohol and water. *Caution*—Ethyl oxide must not be used for anesthesia.

AQUA CHLOROFORMI, chloroform water (U. S. P., B. P.). Dose, 15 cc. (U. S. P.), 15 to 30 mil. (B. P.).

CHLOROFORMUM, chloroform ($CHCl_3$) (U. S. P., B. P.). It contains not more than 99.5 per cent of $CHCl_3$, the remainder consisting of alcohol (U. S. P.). It is trichloromethane to which 1 to 2 per cent of dehydrated alcohol has been added (B. P.). Dose, 0.06 to 0.3 mil.

Chloroform is a clear, colorless, mobile liquid with a characteristic odor and burning taste. It is soluble in about 200 parts of water and is miscible with alcohol and ether. *Caution*—Care should be taken not to vaporize chloroform in the presence of a naked flame, because of the production of noxious gases.

EMULSIO CHLOROFORMI, emulsion of chloroform (B. P.), contains 50 mil. of chloroform in 1000 mil. of water, tragacanth being used as the demulcent. Dose, 0.3 to 2 mil. (Is equivalent in chloroform content to spirit of chloroform (B. P.)).

LINIMENTUM CHLOROFORMI, chloroform liniment (U. S. P.), contains not more than 30.5 cc. of $CHCl_3$ in each 100 cc. of camphor and soap liniment.

SPIRITUS ÆTHERIS, spirit of ether (B. P.), contains 330 mil. of ether in 1000 mil. of alcohol; alcohol content, about 60 per cent. Dose, 1 to 4 mil.

SPIRITUS CHLOROFORMI, spirit of chloroform (B. P.), contains 50 mil. of chloroform in 1000 mil. of alcohol; alcohol content about 85 per cent. Dose, 0.3 to 2 mil.

TRICHTOROÆTHYLENUM, TRICHLORŒTHYLENE (C_2HCl_3) (U. S. P.) contains not more than 99.5 per cent of C_2HCl_3, the remainder consisting of alcohol. It is practically insoluble in water; miscible with alcohol. Dose by inhalation, 1 cc.

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2. Nitrous Oxide

The oldest of the anesthetics, nitrous oxide, N_2O, does not belong to the methane series but may be discussed at this point. Wells first used it clinically in 1846, and Andrews first used it along with oxygen in 1868.

Symptoms.—When a mixture of about 40 per cent nitrous oxide and air is inhaled for a few seconds, a condition resembling alcoholic intoxication is produced with much hilarity and laughter so that the oxide is known popularly as "laughing gas.[1] Even at this point a certain amount of anesthesia is obtained, and it was the observation that persons falling during this stage did not complain of pain that first suggested to Wells

[1] "A young man, a Mr. Davy . . . has made some discoveries of importance, and enthusiastically expects wonders will be performed by the use of certain gases, which inebriate in the most delightful manner, having the oblivious effects of Lethe, and at the same time giving the rapturous sensation of the Nectar of the Gods. Pleasure even to madness is the consequence of this draught." (Maria Edgeworth, 1800.)

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the anesthetic properties of the gas. The action of this concentration is one of analgesia. Davy had noted these general symptoms forty years previously, but his suggestion that nitrous oxide might be used in surgical operations passed unnoticed.

The inhalation of 35 to 70 per cent of nitrous oxide causes after a few seconds a rushing, drumming, hammering in the ears, indistinct sight, staggering gait, and swaying of the body from side to side. The patient seems brighter and more lively and often bursts into laughter. Somewhat later a feeling of drowsiness may come on, but this is not constant; the sensibility to pain is much less acute than normally, but no complete anesthesia is produced by this mixture of gases; the sense of touch is comparatively little altered, although a state of semi-unconsciousness exists. The pupil is generally slightly dilated, the face flushed, and the pulse somewhat accelerated.

In actual practice a mixture of 85 to 90 per cent of nitrous oxide with 10 to 15 per cent of oxygen is employed to produce anesthesia. Details of these effects will be given later, but it should be stated that *plane one* anesthesia with incomplete muscular relaxation is all that is obtained when a nitrous oxide-oxygen mixture is administered. When pure nitrous oxide is inhaled without the admixture of oxygen, the patient passes almost instantaneously through the symptoms already described but then loses consciousness completely; the face is cyanotic, the respiration becomes stertorous and dyspneic and ceases after a weak convulsion, while the heart continues to beat for some time afterwards. If the mask through which the patient has been inhaling the gas is removed when the cyanosis becomes marked, very complete anesthesia lasts for thirty to sixty seconds, and the patient then recovers within a few minutes and suffers from no after effects whatever. No prolonged anesthesia can be produced, however, as the respiration becomes endangered if the mask be kept on longer than the beginning of the cyanotic stage. As a matter of fact, it should be emphasized that pure nitrous oxide should seldom, if ever, be used even for short anesthesia because a fatal effect may result.

Action.—Nitrous oxide supports combustion outside the body for if a glowing splinter of wood be held in it, it bursts into flame exactly as if it were immersed in oxygen. In the tissues of the body, however, nitrous oxide behaves in the same way as any other indifferent gas, such as hydrogen or nitrogen; that is, the tissues exposed to it suffer from asphyxia owing to the oxygen of the air being excluded. Animals die after inhaling nitrous oxide in almost the same time as after hydrogen or nitrogen, and at death the spectrum of the blood shows no oxyhemoglobin to be present, the tissues having used up all the available oxygen. Nitrous oxide, therefore, does not support combustion in the animal body; the nitrogen is not split off from the oxygen at body temperature as it is when the oxide is exposed to high temperatures outside the body.

Nitrous oxide has a special effect on the central nervous system although in the rest of the tissues it acts only by excluding the oxygen; it depresses the brain by virtue of its molecular form just as does chloroform or ether. This has been shown in a variety of ways; thus, if it

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were a perfectly indifferent substance, no more effect would be produced by it when mixed with one-fourth of its volume of oxygen than by air, which consists of one part of oxygen and four parts of an indifferent gas, nitrogen. But 80 per cent nitrous oxide has definite effects on the behavior of animals, and even 73 per cent produces some slowing of the respiration.

The narcotic action was studied by Paul Bert in a series of experiments on man and animals. He noted that only imperfect anesthesia was produced by 80 per cent nitrous oxide while the pure gas produced asphyxia. The problem was to introduce as much gas into the blood as would pass in under pure nitrous oxide and at the same time to supply sufficient oxygen to prevent asphyxia. The absorption of nitrous oxide depends upon its partial pressure in the lungs as it is simply dissolved in the blood without forming any real combination with it, and the quantity absorbed by the blood may be augmented by increasing the barometric pressure. Bert, therefore, administered a mixture of 80 parts of nitrous oxide and 20 parts oxygen to animals in a glass case in which the pressure was raised one-fourth above the ordinary atmospheric pressure. The absorption of the nitrous oxide was the same as if the animal had breathed the pure gas at the ordinary air pressure, and at the same time as much oxygen was absorbed as in ordinary air. The result was apparently a complete anesthesia without asphyxia, which could be maintained for three days without injury to the animal. Kemp has shown that a mixture of oxygen and nitrous oxide can be inhaled for some time and produce anesthesia, which passes off at once when nitrogen is substituted for nitrous oxide. Furthermore, the oxygen contained in the blood at the deepest stage of anesthesia is quite sufficient to maintain life and consciousness were no nitrous oxide present, provided oxygenation is maintained at a proper level. There can, therefore, be no doubt that nitrous oxide has distinct effects on the central nervous system although it is indifferent to the other tissues. The anesthesia is due to a specific action on the nervous tissues although this may be reinforced by the asphyxia present.

Several workers have reëxamined the relationship of nitrous oxide to oxygen in *surgical anesthesia,* and their results in general point to the importance of the oxygen content of the blood as determining the degree of anesthesia taking for granted that there is an adequate concentration of nitrous oxide present. Greene and his co-workers have shown that for light anesthesia in dogs the inhalant mixture must contain not more than 7.6 per cent by volume of oxygen and for deep anesthesia even as little as 3.49 per cent by volume may suffice. For satisfactory surgical anesthesia, about 90 per cent of nitrous oxide is needed, thus a certain degree of anoxemia is always present.

The experiments of Bert described above have also been critically reëxamined by Brown, Lucas, and Henderson, and they are led to question the possibility of securing anesthesia under conditions of increased pressure unless the amount of oxygen is restricted. They therefore concluded that surgical anesthesia with this gas depends not only upon the depressing action of the gas but also upon a certain degree of anoxemia.

Death during nitrous oxide anesthesia probably occurs, not from the direct action of the nitrous oxide on the respiratory center, but from the lack of oxygen although the depression of the center is undoubtedly a contributing factor.

The **Respiratory Center** is depressed when the gas is inhaled in comparatively dilute form for the breathing is slower and deeper even after

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73 per cent. The respiration ceases somewhat earlier under nitrous oxide than under indifferent gases, which would indicate that the cessation of the breathing is due at any rate in part to the specific depressant action. In asphyxia from nitrous oxide there is less convulsive movement than under hydrogen, owing to the general depression of the nerve cells.

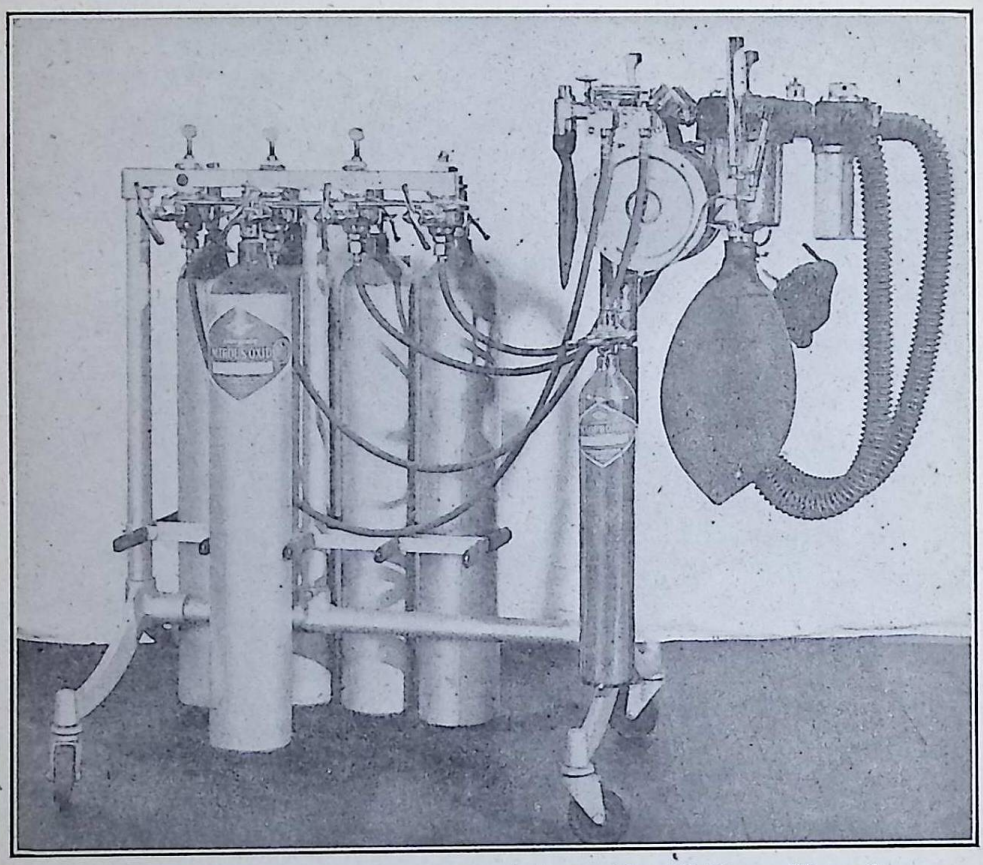

FIG. 21.—A common type of gas anesthesia machine (McKesson Nargraf).

The **Circulation** is little affected by nitrous oxide directly, the rise in the blood-pressure and slowness of the pulse being due to the asphyxial condition of the blood; the pulse is not so slow as in ordinary asphyxia or in asphyxia from nitrogen or hydrogen, because the inhibitory center is less capable of activity. The heart is not affected directly but only by the lack of oxygen.

The **Blood** dissolves more nitrous oxide than water, apparently because it is taken up by the lipids of the corpuscles in the same way as chloroform. About 40 mg. in 100 cc. blood are found at the beginning of anesthesia, 50 mg. in complete anesthesia, and 60 mg. when respiration ceases. It is without doubt the safest of the anesthetics since millions of persons have been subjected to its influence, and only a comparatively few cases of death are reported from its use.

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Practical Anesthesia.—Nitrous oxide is a stable gas at ordinary temperature and pressure and is invariably administered by inhalation from a cylinder into which it has been forced under high pressure. For this purpose, a gas machine is used (see Fig. 21, p. 298) and a tight-fitting mask is fitted over the face. The general principles involved are the same as for those using ether—adequate oxygen supply to the tissues and proper removal of carbon dioxide. With nitrous oxide, it is very important that all nitrogen be washed out of the apparatus since it will interfere with the anesthetic properties of this gas. The "to and fro" method with partial re-breathing is the simplest and the most satisfactory manner of administering gaseous anesthetics. As a rule, a carbon dioxide absorber is added to prevent excess accumulation and rebreathing of this gas (Fig. 22).

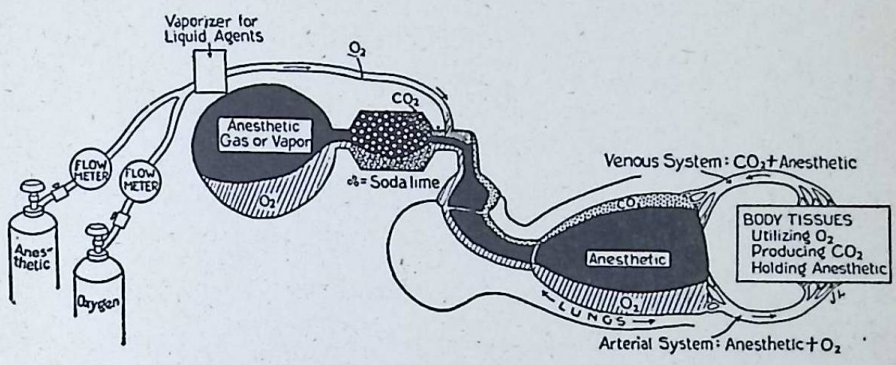

FIG. 22.—The "to and fro" method. (From "Fundamentals of Anesthesia," courtesy of American Medical Association Press.)

For short operations or dental procedures, 5 per cent oxygen added to the nitrous oxide is preferred. Stages of anesthesia are difficult to recognize, but the pupils are usually dilated, the respiration stertorous, the blood-pressure elevated, and the pulse quickened. When cyanosis develops and the respirations become very noisy, the anesthetic is removed and surgical procedures requiring about one minute may be performed. As a rule, the muscular tone is increased at all times and semi-convulsive seizures are not uncommon. When longer periods of anesthesia are required, the inhalation is commenced with pure nitrous oxide, but after ten or fifteen seconds oxygen is admitted and administered in a concentration of 4 or 5 per cent. This amount is gradually increased a little later as signs of deficient oxygenation become more apparent until in two or three minutes a percentage mixture of the gases is found which will produce a satisfactory anesthesia without marked cyanosis. For this purpose, about 90 per cent of nitrous oxide is necessary with 10 per cent of oxygen. It is recommended that morphine and atropine should always be given postoperatively since in a goodly number of instances such premedication will allow as much as 15 to 17 per cent of oxygen to be administered. If anesthesia can be maintained with a lessened concentration of nitrous oxide, such a procedure is preferred. When a satisfactory percentage mixture is found, the narcosis may be continued indefinitely, making only such changes in the mixture as may be indicated by the signs shown by the patient. Clear-cut signs and definite stages of anesthesia are lacking even when nitrous oxide is administered as just described. The most important sign is color which should be maintained as a "good pink" shade. Next in importance is respiration—a soft snore being one of the first signs of satisfactory anesthesia. Muscle tone is always present with incomplete relaxation and even some rigidity since plane one is the upper limit of anesthetic safety when this drug is used. Blood-pressure and pulse remain normal and the

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pupil is somewhat contracted. The corneal reflexes remain intact. Returning consciousness necessitates a diminution in the oxygen; stertor and cyanosis an increase.

This form of anesthesia is admirably adapted for many operations and may be maintained for hours if necessary. The circulation and respiration are less seriously altered than by either chloroform or ether, and the return of consciousness is almost immediate. A great drawback to its use in prolonged operations is that for a safe and satisfactory anesthesia considerable skill is necessary in its administration. Some anesthetists suggest that premedication with tribromoethanol (avertin) makes for easier maintenance. As indicated, muscular relaxation is hard to attain, and this precludes its use in some operations in which, however, it may be employed at first and then be replaced by chloroform or ether, whose preliminary disagreeable effects are thus avoided.

The high blood-pressure induced by nitrous oxide asphyxia is sometimes said to be dangerous in elderly persons from their liability to apoplexy, and of the few fatalities under the gas, several would seem due rather to this than to the drug directly, but the danger is often overstated, and in fact, it is a question whether the shock caused by the operation without gas would not be more dangerous than the effects of the gas itself. No such symptoms arise when the nitrous oxide is administered diluted with oxygen.

Occasionally some glycosuria occurs after the inhalation, not owing to the gas itself but to the accompanying asphyxia. It is merely temporary and has no practical importance.

The treatment of accidents in anesthesia under nitrous oxide consists of artificial respiration alone.

Preparations

Nitrogenii Monoxidum, nitrous oxide (N_2O) (B. P.), contains not less than 93 per cent by volume of nitrous oxide.

Oxidum Nitrosum, nitrous oxide (U. S. P.), contains not less than 95 per cent by volume of N_2O. It is a colorless gas without appreciable odor or taste.

Nitrous oxide dissolves in 1.5 to 2 volumes of water and is freely soluble in alcohol.

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3. Ethylene

Brown and Luckhardt and Carter published the first reports of the anesthetic effect of this substance on animals in 1923, and the latter authors also included preliminary reports of its effects on man, given under laboratory conditions. Very shortly afterward Luckhardt and Carter reported a series of 108 cases in which the gas had been used clinically, and since that time it has been employed quite widely for the production of surgical anesthesia.

Ethylene, $CH_2{:}CH_2$, is a gas at ordinary conditions of temperature and pressure. When a proper mixture with oxygen is inhaled, a state of surgical anesthesia is promptly induced. The action seems to be *intermediate* between ether and nitrous oxide, somewhat resembling ether as

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to depth but nitrous oxide as to rapidity of induction and recovery. The induction period is short, usually with little or no evidence of excitement. After a very few inhalations, the patient loses consciousness and in from one to four minutes, as a rule, is completely anesthetized. Occasionally individuals are found who are refractory to this anesthetic just as they may be to others. With cessation of administration, recovery is also prompt and relatively free from the unpleasant after-effects of ether anesthesia. In order to obtain and maintain full surgical anesthesia, 90 per cent ethylene and 10 per cent oxygen is usually required. With this concentration the relaxation is sufficient for most major operations, but occasionally it may be necessary to supplement the ethylene-oxygen with small amounts of ether vapor. It is said that this addition becomes less frequently required with the development of skill on the part of the anesthetist. Premedication with morphine also makes possible the attainment of a greater degree of relaxation. Often in prolonged operations the concentration of ethylene may be decreased even to 80 per cent without disturbing the even sequence of anesthesia.

The patient under ethylene does not pass through the *stages* of anesthesia noted with ether or chloroform. The concentration of oxygen permitted makes it possible to keep a good color, usually with no trace of cyanosis. Moreover, an occasional increase in oxygen to much higher concentrations than 10 per cent can be permitted for one or two breaths with no resulting irregularity in the depth of the anesthesia. The skin remains dry, there being little or no increase in perspiration and therefore little or no fall in body temperature. The *respiration* is slow and regular, and the pulse, which in most patients is accelerated before induction, gradually falls to normal and remains there. *Blood-pressure* is little affected and the *pupil* is moderately contracted as in sleep. However, *muscular relaxation* is never complete and unless anoxia is produced, a depth of *plane two* anesthesia only is reached. Some surgeons have claimed that anesthesia under ethylene-oxygen produces a wetter field for operation, *i. e.*, due to capillary oozing. In the hands of a good anesthetist, this claim cannot be substantiated.

When the anesthetic is removed, recovery is very prompt, the patient frequently regaining consciousness while on the table. Some retching movements or actual vomiting may occur on awakening, and about one-third of all patients vomit sometime during the first three or four hours. Luckhardt found that about 30 per cent showed nausea and vomiting during this period as compared with about 75 per cent in a similar series using ether. Vomiting, when it does occur, is rarely severe or prolonged, and post-anesthetic gas pains are very much less frequent and less severe than with ether. It is believed by some that the presence of impurities in the ethylene may have something to do with the incidence of emesis.

From the pharmacological standpoint, ethylene-oxygen anesthesia is interesting in that a satisfactory degree of suppression of consciousness and of the reflexes can be produced with scarcely any effect upon other functions. The *vasomotor center* seems scarcely to be affected although with prolonged anesthesia there may be a slight fall in blood-pressure

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(10 to 15 mm. Hg., Luckhardt). If the concentration is increased to a toxic point, the respirations are increased for a time due to the asphyxia and then fail, but at this time the circulatory mechanism is in good condition so that prompt recovery results from the administration of artificial respiration. Death due to the gas itself is extremely rare, and if it occurs, it may more properly be said to be due to asphyxia. According to Miller and Plant, there is an increase in amplitude of contractions of the stomach, small intestines, and colon during light anesthesia from ethylene which lessens or returns to the normal with full surgical anesthesia. There is little, if any, irritation of the mucous membranes of the nasopharynx, and therefore no excessive secretion of saliva or mucus. Nor is there any evidence of any kidney injury even after repeated and prolonged administration. The *elimination* of the gas seems to be entirely through the lungs, and none of it is altered or combined in the body.

The *advantages* of ethylene are evident from the above discussion. It acts promptly, gives a greater degree of relaxation than nitrous oxide but less than ether, is not irritant, permits of sufficient oxygen being given to avoid asphyxia, and is relatively free from unpleasant after-effects. It has been used not only in all types of general surgery but in the specialized fields of genito-urinary surgery, obstetrics, and dentistry.

It has the practical disadvantage of forming explosive mixtures with air, which precludes its use in the presence of the open flame, cautery, or electric spark. Recent evidence indicates, however, that as a rule, because of its rapid diffusibility, explosive concentrations of ethylene (3.2 per cent) exist no closer than two feet from the mask. If adequate ventilation of this area is carried out, the risk of explosibility is largely reduced. Two other measures which have been adopted to minimize the dangers are humidification of the atmosphere of the room and electrical grounding of the anesthesia apparatus and operating table. A few explosions have resulted from the use of this drug, presumably being caused by a discharge of static electricity developing within the anesthetic machine. However, with modern methods, this risk is small and is greatly overshadowed by the advantages which ethylene possesses.

Preparations

Æthylenum, ethylene ($CH_2=CH_2$) (U. S. P.), contains not less than 99 per cent by volume of C_2H_4. It is a colorless gas with a sweet odor and taste.

Æthylenum, ethylene (C_2H_4) (B. P.), contains not less than 98 per cent by volume of C_2H_4.

Ethylene dissolves in about 9 volumes of water and 0.5 volume of alcohol at 25° C.

Caution.—Ethylene is inflammable, and a mixture of it with oxygen or air will explode when brought in contact with a flame or other causes of ignition.

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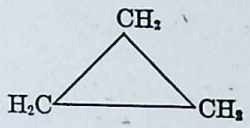
4. Cyclopropane

This substance was first prepared by Freund in 1882, but no particular use was found for it until 1929 when Lucas and Henderson published their findings on its anesthetic properties. Waters and Schmidt in 1934 first reported its use clinically, and since that time its popularity has increased in spite of certain disadvantages which it possesses. Cyclopropane is a *gas* which is heavier than air, having a specific gravity of 1.46 and a structural formula:



It is almost insoluble in water but is very soluble in lipids. It is inflammable and is capable of exploding when mixed with oxygen in concentrations as low as 3.8 per cent. This property makes it important to take precautions against using it in the neighborhood of a flame and cautery. Special care should likewise be taken against the production of electrostatic sparks since cyclopropane is potentially explosive when used as an anesthetic with oxygen.

Cyclopropane will produce narcosis when inhaled in concentrations as low as 4 per cent, but much higher concentrations are generally used, depending upon the depth and duration of anesthesia required. As a rule, 15 per cent of cyclopropane is required for complete anesthesia which is reached in about three minutes. The gas may be given by the closed carbon dioxide absorption technique in which the mask is supplied with oxygen and cyclopropane, the latter being shut off after one to three minutes. Narcosis takes place in a few minutes as the gas becomes distributed in the tissues. Oxygen is then supplied according to the needs of the patient, and if necessary, further cyclopropane may be added if the anesthesia is insufficient. In the administration of the gas, care must be taken not to increase its concentration too rapidly as time is needed for adequate distribution in the tissues. The gas is quite potent and high concentrations can be inhaled without irritation and without much change in respiration until a stage of very distinct depression is reached. Muscular relaxation is less complete than with ether but is greater than with nitrous oxide and ethylene. However, *plane three* is easily reached by the proper administration of this anesthetic. Upon removal of the mask, recovery is rapid and complete in a few minutes.

The ordinary signs of anesthesia under cyclopropane are not as useful as with other anesthetics. *Respiration* is not affected until depression occurs. The *pupil* is often dilated in spite of morphine premedication. Color is unimportant during anesthesia since adequate oxygen usually prevents the appearance of cyanosis which would indicate toxic effects.

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Blood-pressure likewise is little altered, and the pulse becomes the best indication of the condition of the patient. A bradycardia of 60 or less makes it essential to lessen the concentration of the gas. If arrhythmias develop, the gas should be removed and oxygen given. The action of cyclopropane on the heart causing irregularities somewhat resembles chloroform since Robbins and co-workers have shown that it increases the irritability of the heart muscle. In addition, epinephrine is likewise contraindicated since the effects of the two drugs may result in ventricular fibrillation. These authors also recommend that one of the barbiturates should always be used for premedication in cyclopropane anesthesia to reduce the chance of cardiac irregularities. In the dog, morphine is also claimed to increase the possibility of cardiac irregularities under cyclopropane anesthesia. Pituitrin is also synergistic with cyclopropane in the production of cardiac arrhythmias, and the two should not be used together (Belinkoff).

In the recovery stage nausea and vomiting are usually slight. Those experienced in its use prefer it to ethylene and in many cases also to ether. It may also be used introductory to the use of ether. It is not irritant or unpleasant or deleterious to the liver, and pulmonary complications probably occur less often than with ether. Cardiac arrhythmias occur which are not usually seen with ether and post-anesthetic headache is not uncommon. Many surgeons prefer cyclopropane in thoracic surgery because of its slight effect upon respiration. It is also useful in conditions which require a complete supply of oxygen to the tissues, such as in anemia, congestive heart failure, and respiratory diseases causing respiratory obstruction. In obstetrics, it is fast becoming the anesthetic analgesic of choice because fetal respiration is not deranged. It is, therefore, a suitable anesthetic agent when used cautiously by those fully informed of its properties, potential dangers, and signs which indicate the stages of anesthesia.

Propylene is too toxic to make it useful in clinical anesthesia.

Preparations

Cyclopropanum, cyclopropane (C_3H_6), (U. S. P., B. P.), contains not less than 99 per cent by volume of C_3H_6. It is a colorless gas with a petroleum benzin odor and pungent taste. It is soluble in about 2.7 volumes of water and freely soluble in alcohol.

Caution.—Cyclopropane is inflammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition.

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5. Tribromoethanol

Tribromoethanol (Avertin).—Tribromoethanol (CBr_3CH_2OH), synthesized by Willstätter in 1923, was introduced into medicine as a hypnotic and general anesthetic by Duisberg in 1926. It was first used as a general anesthetic, but since its actions once established are difficult of alteration, it should never be used for this purpose. As a basal narcotic, it is useful in general anesthesia and is hence considered in this section.

Chemically, it is related to alcohol and chloral hydrate. It occurs as a white powder and is relatively stable in air, but exposed to light it hydrolyzes, yielding hydrobromic acid. Consequently, it is always packed in dark bottles.

As a rule, 80 mg. per kg. of body weight is administered rectally. The official preparation is a solution in amylene hydrate, which also possesses hypnotic properties, and each basal dose of tribromoethanol contains 40 mg. of this solvent. *Absorption* is quite rapid, 50 per cent being absorbed in the first ten minutes, 95 per cent in twenty-five minutes. The average duration of hypnosis is two and one-half hours. The concentration in the nervous tissues quickly reaches a maximum and remains after complete disappearance from the blood. *Elimination* is chiefly through the kidneys, in a conjugated form with glucuronic acid. Seventy-five per cent is eliminated in forty-eight hours, but it requires approximately seven days for complete excretion to take place. Amylene hydrate is eliminated unchanged through the lungs and kidney.

Its *action* is predominantly that of central nervous system depression, but occasionally excitation is observed with small doses and as an initial effect with larger doses.

Avertin generally causes a greater depression of the *respiratory center* than ether or chloroform, a fact which is of some significance when it is used with pre-anesthetic medicaments such as morphine. A temporary slight fall in *blood-pressure* is also often encountered although the *pulse rate* may be increased. In one series of patients, this was found to parallel a decrease in blood volume. After much larger doses a depression of the vasomotor center and injury to heart and blood-vessels have been described. Degenerative changes in the liver, kidney, and colon and acidosis have been reported after doses greater than those now recommended and some authorities consider preëxisting pathology of these organs a contraindication to its use. In addition, general *metabolic processes* are diminished about 15 per cent, and glycogen stores in the liver are considerably depleted. Intracranial pressure is decreased, thus making it valuable as an adjunct anesthesia in neurosurgery. The *pupils* constrict, but ordinary eye and other reflexes are not abolished. An increase in blood sugar is the rule, but this is not usually mirrored in the secretion of urine. Tribomoethanol does cause albuminuria in 20 per cent of the cases and should be used with caution in hepatic

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disease. Clotting time is increased which may be a disadvantage in certain operations.

Used as a *basal hypnotic*, induction is pleasant, and the mental distress and irritation of the respiratory tract involved in the induction of anesthesia by volatile anesthetics are avoided, and it is generally agreed that vomiting is less frequent than after ether or chloroform. Furthermore, an amnesia usually occurs extending from the beginning of induction until several hours after the operation. Of course, avertin has the disadvantage common to all non-volatile anesthetics of the lack of control of its action following administration. Also close nursing attention is required postoperatively to prevent respiratory accidents such as the falling back of the tongue.

No satisfactory conclusion is yet possible concerning the relative safety of avertin in comparison with other anesthetics, but being a halogenated compound, it may damage the liver. A number of deaths have been reported following its use, but most of them have been due to doses larger than recommended for basal narcosis. Under no circumstance should the dose of the solution of tribomoethanol exceed a total of 6 to 8 cc. for women and 9 to 10 cc. for men, regardless of weight.

Its chief *uses* as a basal anesthetic prior to general anesthesia are in neurosurgery, pulmonary disease, and biopsy procedures. Experience in its use is of paramount importance, and it should never be administered without a full appreciation of its toxic potentialities. Aside from its use in general surgery, it has been used successfully in smaller doses (60 to 70 mg. per kg.) in obstetrics during the second stage of labor, but this is probably not a wise procedure. Favorable results have also been reported from moderate repeated doses in the control of maniacal attacks, status epilepticus, and eclampsia. Recently, it has been employed with good results in the treatment of tetanus. In this condition, it is used for the control of the muscular rigidity and convulsions, in conjunction with large doses of tetanus antitoxin. The tribromoethanol is given by rectal injection in a sufficient dose to produce relaxation and quiet and is then repeated at intervals, of six to eight hours as required. It may be necessary to keep the patient under the influence of diminishing doses of the drug for several days. *Contraindications* to the use of tribromoethanol include hepatic and cardiac disease, shock, old age, acute pulmonary tuberculosis, obesity, enteritis, acidosis, and marked hypothyroidism.

General anesthesia produced by alcohol (p. 266) has already been discussed. The intravenous use of barbiturates (pentothal sodium and evipal) to cause complete unconsciousness will be taken up under the section of hypnotics (p. 310).

Preparations

Liquor Tribromoæthanolis, solution of tribromoethanol (U. S. P.), a solution of tribromoethanol in amylene hydrate containing in each 100 cc. not less than 99 grams and not more than 101 grams of $C_2H_3Br_3O$. Dose, for each kilogram of body weight, 0.06 cc.

Caution.—The total amount administered should not exceed 8 cc. for women or 10 cc. for men, regardless of weight.

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TRIBROMOÆTHANOL, tribromoethyl alcohol ($Br_3C.CH_2OH$) (U. S. P.), contains not less than 99 per cent $C_2H_3Br_3O$. It is a white crystalline powder with a slight aromatic odor and taste and is unstable in air and light. One gram is soluble in about 35 cc. of water, and it is very soluble in amylene hydrate. Dose, rectal (for each kilogram of body weight), 60 mg.

Caution.—The total amount administered should not exceed 8 grams for women or 10 grams for men, regardless of weight.

ALCOHOL TRIBROMOETHYLICUM, tribromoethyl alcohol (B. P.). (See Tribromoæthanol (U. S. P.).) Dose, by rectal injection, 0.075 to 0.1 gram per kilogram of body weight.

BROMETHOL, bromethol, solution of tribromoethyl alcohol (B. P.). A solution of tribromoethyl alcohol in amylene hydrate. Each mil. contains 1 gram of tribromoethyl alcohol. Dose, by rectal injection, 0.075 to 0.1 mil. per kilogram of body weight.

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Special Considerations

A résumé of the chief aspects of the most important general anesthetics is given in the accompanying Table, but a discussion of certain other factors common to all seems pertinent at this point.

Much has been written regarding the relative advantages of local and spinal methods as compared to the inhalation method of producing anesthesia. Many surgeons feel that no argument exists since the general anesthetics absolutely prevent nervous apprehension and anxiety in the operating room. Furthermore, the techniques of spinal and similar types of anesthesia require more exacting techniques, and the potential dangers are greater. Although nitrous oxide, ethylene, cyclopropane, and vinethene are being used with increasing frequency, ether is still used extensively after induction with some more pleasant agent. Chloroform, because of its untoward effects, is now little used. Tribromoethanol in experienced hands has proven valuable as a basal anesthetic.

The value of **Premedication** is of great importance in general anesthesia, but no standardized procedure should be adopted since each case presents an individual problem. In general, drugs are administered before anesthesia to allay psychic fear and apprehension, to depress secretory activity, to decrease oxygen consumption, and to reduce the amount and concentration of the anesthetic used. Many anesthetists feel that pre-anesthetic medication should only be used if the anesthetic is to be administered by the closed method since respiration is unfavorably depressed by morphine when open or semi-open methods are used. This need not be true if the dose of morphine, atropine, scopolamine, and barbiturate be judiciously chosen. As a rule, the usual hypnotic dose of barbiturate is given the night before the operation and repeated

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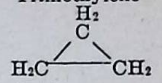
Comparison of the Most Important General Anesthetics

Common name	Ether (U. S. P., B. P.)	Chloroform (U. S. P., B. P.)	Nitrous Oxide (U. S. P., B. P.)	Ethylene (U. S. P., B. P.)	Vinethene (N. N. R.)	Cyclopropane (U. S. P.)
Chemical name	Diethyl ether	Trichloromethane	Nitrous oxide	Ethylene	Divinyl ether	Trimethylene
Formula	$C_2H_5.O.C_2H_5$	$CHCl_3$	N_2O	$CH_2{:}CH_2$	$CH_2{:}CH.O.CH{:}CH_2$	
Specific gravity	2.56	4.10	1.52	0.97	2.42	1.45
Stability	Satisfactory	Satisfactory in colored bottles	Stable under pressure in steel containers	Stable under pressure in steel containers	Not stable after opening	Stable under pressure in steel containers
Inflammability and explosibility	Inflammable and explosive	Non-inflammable	Non-inflammable	Inflammable and explosive	Inflammable and explosive	Inflammable and explosive
Time for induction	10 to 30 minutes	4 to 12 minutes	1 to 4 minutes	1 to 4 minutes	5 to 12 minutes	½ to 3 minutes
Time for recovery	About 30 minutes	About 20 minutes	2 to 3 minutes	1 to 3 minutes	3 to 4 minutes	3 to 6 minutes
Pleasantness of induction	Unpleasant	Relatively unpleasant	Pleasant	Pleasant, but odor unpleasant	Slightly unpleasant	Pleasant
Muscular relaxation	Excellent	Excellent, but less than with ether	Never complete—Plane 1 only reached	Relatively good, but Plane 2 only reached	Good	Good
Effect (locally) on respiratory tract	Most irritant	Relatively irritant	None	None	Moderate irritation	Only slight irritation
Effect on respiration	Early stimulation—depression if pushed	Early stimulation—depression if pushed	Stimulation if anoxemia present	Stimulation if anoxemia present	Early stimulation—depression if pushed	None except depression when pushed
Effect on heart *a.* Pulse rate	*a.* Early increase, slowed when pushed	*a.* Early increase, slowed when pushed	*a.* None except induction stage increase	*a.* None except induction stage increase	*a.* None of importance	*a.* Apt to cause arrhythmias; some slowing
b. Depression of cardiac muscle	*b.* None	*b.* Toxic to myocardium. Light anesthesia may cause ventricular fibrillation	*b.* None	*b.* None	*b.* None	*b.* Little if any
Effect on blood-pressure	Slight increase early	Gradual fall during anesthesia	Increased early	Increased early	None during anesthesia	None if respiration is normal
Liver damage	None	Possible after long operations especially	None	None	May occur	Questionable
Chief contraindications	Respiratory infections. Acidosis	Hepatic, renal and cardiovascular disease	Old people	Old people	Hepatic disease	In the presence of cardiac irregularities
a. Blood mg./per cent for anesthesia	*a.* 100–140	*a.* 25–35	*a.* 50	*a.* 140	*a.* 18	*a.* 16–20
b. Concentration inhaled for anesthesia	....	....	*b.* 85–90 with 10–15 per cent of oxygen	*b.* 80–90 with 10–20 per cent of oxygen	....	*b.* 15 with 85 per cent of oxygen
Preferred method of administration	Open-drop or vaporized	Open-drop	Gas machine	Gas machine	Gas machine	Gas machine
Postoperative effects	Most marked of all. Vomiting and ileus	Less than ether	Few if any	Less than chloroform	Headache; vomiting less than ether	Vomiting and distention less than ether
Relative potency	100	100	15	25	100	100

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early on the next morning. In addition, 10 to 16 mg. of morphine plus 0.4 mg. of atropine or scopolamine are administered thirty to forty-five minutes prior to the administration of the anesthetic. Whether scopolamine or atropine is to be preferred depends chiefly upon the experience of the anesthetist and surgeon since in the dose used it is doubtful if scopolamine contributes greatly to increased respiratory depression as compared with atropine. The decrease of mucus during ether and vinethene by the previous administration of atropine is helpful, but it may be a factor in the increased formation of atelectatic plugs. With other general anesthetics, neostigmine and morphine may be superior (see Morphine, p. 316). Preoperative medication is especially valuable prior to nitrous oxide and ethylene anesthesia since the concentrations necessary are considerably reduced. Barbiturates also have this property which will be discussed later (see p. 329). The use of tribromoethanol has already been mentioned (p. 306). Preoperative medication given properly has no significant effect on the usual signs of anesthesia except one may always expect the pupil to be contracted in planes one and two when morphine or a combination of morphine and atropine is used.

In the elderly patient ether is perhaps still the safest anesthetic in the hands of the inexperienced, but cyclopropane is probably the agent of choice. Nitrous oxide and ethylene should be avoided because of the danger of anoxia.

The most recent adjunct in general anesthesia has been the use of curare in the form of an assayable commercial extract known as "intocostrin." The pharmacology of curare will be discussed later (p. 423), and it will suffice at this point to repeat that its principal action consists in preventing the effector substance of voluntary muscle from reacting to acetylcholine. However, until McIntyre obtained a substance free from the undesirable side effects of ordinary curare, clinical use of this drug was not possible.

According to Cullen, "intocostrin" should not be used to produce increased muscular relaxation in cases where incomplete relaxation is due to poor choice of the anesthetic, faulty technique, or ignorance of the physiology and pharmacology associated with anesthesia. He recommends it when it is not possible to attain sufficient relaxation except by increasing the concentration of the anesthesia to a near-toxic level.

In practice, "intocostrin" is administered intravenously once the second plane is reached or when the abdominal skin incision is made. Most adults tolerate 0.060 gram (3 cc.) of "intocostrin" as an initial dose. As much as 0.100 grams total may be given if muscular relaxation is not complete. Respiration is usually depressed by doses necessary to cause muscular relaxation, but it only lasts about five minutes.

Curare has chiefly been used with cyclopropane anesthesia, and it is believed that it may somewhat decrease the possibility of arrhythmias due to this gas, but experimental data on this point is not conclusive. Curare has also been used with nitrous oxide, ethylene, and ether anesthesia. With ethylene, larger doses are needed and respiratory depression is more marked. When ether is the anesthetic agent, the dose of

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curare must be reduced by one-third as compared to the amount used with cyclopropane since ether *per se* possesses a curariform action.

Usual premedication techniques are employed when curare is used and no interference with the anesthesia has been noted. No post-anesthetic complications have been reported when curare is used, but it should be emphasized that neostigmine, its direct antagonist, should be immediately available at all times if respiration becomes dangerously depressed.

In the hands of the skilled anesthetist, curare will prove a valuable adjunct in inhalation anesthesia, provided its potential dangers are always kept in mind.

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III. SEDATIVES AND HYPNOTICS

1. Chloral Group

Some twenty years after the introduction of the anesthetics, a new interest was given to the methane series by the examination of chloral hydrate ($CCl_3CH(OH)_2$) by Liebreich. Henceforth, the attention of investigators was diverted from the quest of anesthetics to that of hypnotics with the result that a number of valuable drugs have been added to therapeutics. These compounds have the same general action as the anesthetics but are used only to produce the first effects of imperfect consciousness or sleep. The anesthetics might be used for this purpose were it not for the comparatively short time during which their action persists. Hypnotics are required to produce a slight but lasting effect, and for this purpose the gradual absorption from the bowel is better adapted than the rapid absorption and equally rapid elimination by the lungs. The narcotics are, therefore, less volatile than the anesthetics and ought to be soluble in water and not irritant in the stomach so as to permit of rapid absorption. The most widely used members of this group are *chloral, phenobarbital,* and other barbiturate derivatives, but many others have received attention.

They all resemble each other in their *general hypnotic* action, and that of choral may be taken as typical of all; in their other characters some differences are presented and these will be taken up for each individual drug. Larger doses of some of these hypnotics have been used to produce general anesthesia, but at the present time they are not used for this purpose but are administered in order to induce a hypnotic effect prior to the administration of anesthetic.

Symptoms.—Chloral in 1 to 2 gram doses produces drowsiness and weariness which soon pass into a condition resembling natural sleep very closely, from which the patient can be awakened by ordinary means, such as touching, loud sounds, or pain. The respiration and

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pulse are rather slower than in waking moments but scarcely more so than in natural sleep, and the somewhat narrowed pupil and unaltered excitability of the reflexes are also common to both conditions. As a general rule, the sleep passes off in five to eight hours and leaves no unpleasant results, but sometimes headache, giddiness, and confusion are complained of. Occasionally, no real sleep is produced by chloral, a condition exactly resembling alcoholic intoxication following its administration and continuing for some time.

When larger quantities, 5 grams, are taken, the sleep is much deeper, the patient cannot be aroused to complete consciousness, the reflexes are distinctly lessened, and the sensation of pain is less acute although no complete anesthesia is present. The respirations are fewer, and the pulse may be slow and somewhat weak. The sleep lasts very much longer (ten to fifteen hours), and nausea, vomiting, headache, and confusion often remain after consciousness is regained. In still larger quantities, chloral produces a condition resembling the third stage of anesthesia. The reflexes are entirely absent, and no movement is elicited by painful operations; the muscles are completely relaxed, the respiration and pulse are both slow and weak, and eventually asphyxia occurs from paralysis of the respiratory center. The heart continues to beat for a short time after breathing ceases. The pupil is often contracted to pinhole size before death in fatal poisoning.

Action.—The Central Nervous System is depressed and eventually completely paralyzed by chloral and its allies. Unlike the anesthetics and alcohol, however, chloral rarely causes excitement. The results of psychological experiments on the effects of small doses of the narcotics seem to indicate that they all depress the sensory or receptive functions of the brain while its motor activity is much reduced by chloral and sulfonal but may appear to be actually increased by paraldehyde; this apparent stimulation is analogous to that under alcohol and may be explained by lessened control. The sleep induced by the dulling of the perceptions may be interrupted by more intense stimuli from without. In particular, acute pain may prevent sleep after chloral, which seems to have no specific effect on pain sensation such as is possessed by morphine. In larger quantities, however, even very great disturbance of the environment produces no interruption of the sleep, and the reflex response to irritation is very much lowered. The motor areas of the brain cortex are rendered less irritable by chloral and eventually fail to react to the strongest electrical stimulation. The *reflexes* of the spinal cord are depressed and finally paralyzed before the failure of the respiration; this depressant action on the spinal reflexes is much more marked than that seen under morphine. The last part of the central nervous system to be attacked is the medulla oblongata for although the respiration is somewhat slower and shallower after small quantities, it is scarcely more affected than in ordinary sleep, and both the excitability of the center and the volume of the inspired air are very similar in the two conditions. As the dose is increased, however, the respiration becomes very slow and weak and finally ceases from paralysis of the center.

The **Heart** is slower after chloral in moderate doses but scarcely more

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so than in natural sleep. There is often some flushing of the face and head from some obscure central action, but the blood-pressure is little affected in the therapeutic use of the drug. In poisoning, the *blood-pressure* is reduced by weakness of the vasomotor center and of the heart, the latter manifesting itself also on slowing of the pulse. This action on the circulation from poisonous doses is more in evidence under chloral than under the other hypnotics which do not contain chlorine. The same difference is met with in ether and chloroform, of which the latter affects the circulation more strongly. The action on the heart in chloral poisoning resembles that of chloroform, the auricles being affected sooner than the ventricles and the strength of contraction failing more than the rate.

Locally, chloral has an irritant action and hence must always be prescribed in dilute solutions to prevent nausea and vomiting. This irritant action induces redness and even vesication when chloral is applied to the skin. It is rapidly absorbed when given by the mouth and is carried to the central nervous system where it is taken up by the cells until they contain more than the blood corpuscles or the cells of other organs, such as the liver.

The effects of chloral on the *tissues* have been found to correspond to those of chloroform in character but are very slight. Fatty degeneration of various organs has been caused in animals by prolonged administration of large doses with evidence of renal involvement as manifested by the appearance of red cells and casts in the urine. Chloral was formerly supposed to lead to glycosuria, but the reducing action of the urine of patients following the administration of chloral is due to chloral itself or a substance derived from the drug rather than to glucose.

It has generally been accepted that chloral is reduced in the tissues to trichloroethyl alcohol (CCl_3CH_2OH), which combines with glycuronic acid to form urochloralic acid, and is excreted in this form in the urine, but this is denied by Lehmann. He has pointed out that if trichlorethanol was formed the action of chloral hydrate would necessarily be much longer since the extra step involved in the detoxification of trichlorethanol would require a longer period of time. Lehmann and Knoefel are of the opinion that chloral combines directly with glucuronic acid, but how much combines in this way and whether the reaction product is excreted or further modified has not been determined. Some escapes by the kidneys unchanged, however, and some is thrown into the stomach, and this may contribute to the nausea and discomfort felt after awaking in some cases.

The old idea that solutions of chloral hydrate and alcohol resulted in the formation of a toxic compound, *chloral alcoholate*, is no longer held. As a matter of fact, the LD_{50} dose for chloral alcoholate is 0.08 gram more than for chloral hydrate alone. If alcoholic solutions of chloral hydrate are administered, the absorption of the chloral is increased, but it is doubtful if chloral alcoholate can be formed in the body (Adams).

The other hypnotics of this series, with the exception of chloralose, have effects similar to chloral as far as their action on the central nervous system is concerned. The chief difference in their effects is seen in the circulation and metabolism, which are even less affected by those which do not possess substituted chlorine atoms.

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Paraldehyde $(CH_3 \cdot CHO)_3$, a polymer of acetaldehyde, resembles alcohol in its effects though it is a much more powerful hypnotic and rarely induces any symptoms of excitement. It does not affect the heart directly even in large doses and has no such effects on the protein metabolism as have been observed under the prolonged administration of chloral; the *pulse* is slightly slower and the *carbonic acid* exhaled is less than normally, but these changes are due to the muscular movements being lessened and are hardly greater in extent than occur in natural sleep. Although very large quantities have been taken without fatal results, and in fact without any more serious consequences than prolonged unconsciousness, this drug accidentally given in too large quantities has not infrequently been the cause of death (MacFall, McDougall and Wyllie, Kotz, Shoor and others).

Deaths have been reported from the ingestion of 25 cc. and the rectal injection of 12 cc. One might consider that the variability in amounts causing a fatality could be explained on rate of absorption or upon an idiosyncrasy to the drug. It is recognized that the latter factor plays little if any part in the toxicity of paraldehyde. However, since 80 per cent is believed to be destroyed in the liver, presence of hepatic dysfunction presumably might be of great importance since impaired function of this organ would delay the absorption and destruction of paraldehyde and thus increase its toxicity.

The intravenous use of paraldehyde as an analgesic has been recommended but such a procedure is fraught with danger. In doses of 1 cc. (total) to 0.5 cc. per kilogram, a marked rise in pulmonary pressure with a concomitant fall in systolic blood-pressure occurs with dilatation and weakening of the right ventricle (Springer *et al.* and Burnstein). One-third of the animals died with the larger dose, and at autopsy pulmonary edema with hemorrhage, a dilated right heart, and edema of all viscera were characteristic findings. These changes are similar to those observed also at necropsy on humans dying from paraldehyde poisoning. Hence, this drug does possess potential untoward effects and should be used cautiously in clinical practice. The toxicity of the drug in many instances is probably due to polymerization products of acetaldehyde (Hemphill and Heller).

Paraldehyde is *excreted* in part by the lungs though mainly in the urine, and the odor remains in the breath for some time after the patient awakens. Paraldehyde has a most unpleasant odor and a hot, burning taste, which renders its administration somewhat difficult. It may perhaps be best given on cracked ice or in iced wine. It may also be given by the rectum, and this route is particularly practical in maniacal or otherwise disturbed patients.

Sulfonmethane (sulfonal) $((CH_3)_2C(SO_2C_2H_5)_2)$ and **Sulfonethylmethane** (trional) $(C_2H_5CH_3C(SO_2C_2H_5)_2)$ are members of a group of the less important hypnotics. They have no immediate action on the *circulation* even in large doses though it is stated that their prolonged use is deleterious to the heart. They are practically tasteless powders and are, therefore, easily taken, but their insolubility in water renders their absorption slow and uncertain, and sleep is therefore late in following their administration, while on the other hand, depression, drowsiness and lack of energy are often complained of the day after. There is some evidence that they exercise a deleterious effect on the liver for the relation of urea to the total nitrogen of the urine is changed and the metabolism of the purine bodies is also affected.

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The use of the sulfonal group, especially when prolonged, has led in many cases to a series of symptoms, the most characteristic of which is the appearance in the urine of a reddish-brown pigment, *hematoporphyrin*, an iron-free product of the decomposition of hemoglobin. Presence of this substance in the urine is a bad prognostic sign since unless it is recognized early, death may occur if the drug is not stopped. Due to the fact that these drugs are destroyed or eliminated so slowly, there is a marked tendency to produce cumulative effects with symptoms of chronic poisoning. For this reason, they are not suited for prolonged administration and hence are now rarely used.

Butylchloral Hydrate ($C_3H_4Cl_3CH(OH)_2$) is similar in action to chloral hydrate, but it is less irritating to the stomach.

Chloralose ($C_8H_{11}Cl_3O_6$) is prepared by heating anhydrous glucose ($C_6H_{12}O_6$) with anhydrous chloral (CCl_3CHO). It acts much more like morphine than like chloral, depressing the psychical functions while increasing the reflexes until convulsions resembling those of strychnine may be produced. The heart is comparatively little affected, and the respiration remains strong unless very large doses are given. In man, it induces sleep, which is sometimes attended by distinctly exaggerated reflexes, especially when large doses are given. The use of this drug is largely confined to animal experimentation. It is not used clinically to any extent.

Amylene Hydrate, or dimethylethylcarbinol ($(CH_3)_2COHCH_2CH_3$) is closely allied to paraldehyde in its effect, but its use is limited to a solvent for tribromoethanol in which case it adds to the narcotic action of "avertin."

Urethane, or ethyl carbamic ester (ethyl carbamate) ($CONH_2OC_2H_5$), is chemically related to urea and to carbromal. In man, its hypnotic actions are weak and inconstant, but it may be worthy of a trial in slight degree of sleeplessness. For the most part, it is now used as a laboratory anesthetic for animals. It has the advantage in that the blood-pressure is not much affected, physiological reflexes remain active, and regular respiration is maintained. The recommended adult dose is about 2 grams, and in addition, the U. S. P. lists an ampule containing about 2 parts of quinine dihydrochloride and 1 part of urethane for use as an injectable sclerosing agent. Urethane is also used in leukemia.

Chlorobutanol (chloretone) trichlortertiary-butylalcohol ($CCl_3C(CH_3)_2OH$), resembles chloral in most respects but is less liable to irritate the stomach. Very large doses have been swallowed without producing any untoward symptoms, but the hypnotic effect is obtained by the use of smaller doses than are necessary in the case of chloral. It paralyzes the terminations of the sensory nerves when it is applied locally and has proved of value as a local anesthetic but is not used much clinically for this purpose although it can be injected as a saturated solution. For a review of the effects of this drug on respiratory processes, see Michaelis and Quastel.

Tolerance is soon acquired toward several of these drugs and when it is developed for one, larger doses of any of the others are required in order to produce sleep. Tolerance for alcohol also involves the use of larger quantities of the hypnotics and in fact often leads to the complete failure of any except the most powerful.

Not infrequently the hypnotics lead to skin eruptions, especially when used for some time. These assume various forms, most commonly erythema, but urticaria, purpura, papular eruptions, and blisters may also occur.

Habit.—Prolonged abuse of chloral leads to a condition somewhat resembling that seen in chronic alcoholism or morphinism and marked by general depression and cachexia, with impairment of the mental powers, digestive disturbance, and exanthemata. The sudden withdrawal of the drug in these cases has sometimes led to symptoms resem-

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bling those of delirium tremens. Cases of sulfonal and paraldehyde habit have also been reported.

Preparations

Amyleni Hydras, amylene hydrate, tertiary amyl alcohol ($C_5H_{12}O$), U. S. P., B. P.), a clear colorless liquid with a camphor-like odor and burning taste. One gram dissolves in about 8 cc. of water. It is freely miscible with alcohol. Dose, 2 to 4 mil. (B. P.).

Chloralis Hydras, chloral hydrate ($CCl_3.CH(OH)_2$), (U. S. P., B. P.), occurs as colorless, transparent or white crystals with an aromatic, penetrating odor and a slightly bitter taste. It slowly volatilizes exposed to air. One gram dissolves in 0.25 cc. of water and in 1.3 cc. of alcohol. Dose, 0.6 gram (U. S. P.), 0.3 to 1.2 grams (B. P.).

Chlorobutanol, chlorbutol, acetone-chloroform (U. S. P.), Chlorbutol (B. P.), ($(CH_3)_2C(CCl_3)$ OH), colorless crystals with a musty somewhat camphor-like taste. One gram is soluble in about 125 cc. of water and in 1 cc. of alcohol. Dose, 0.6 gram (U. S. P.), 0.3 to 1.2 grams (B. P.).

Methylsulphonal, methylsulphonal ($(CH_3)(C_2H_5)C(SO_2.C_2H_5)_2$), (B. P.) occurs as a lustrous, white, odorless slightly bitter powder soluble in 320 parts of water and in 12 parts of alcohol. Dose, 0.3 to 1.2 grams.

Paraldehydum, paraldehyde ($C_6H_{12}O_3$), (U. S. P., B. P.), is a colorless transparent liquid with a strong pungent odor and a disagreeable taste. One cc. is soluble in about 8 to 9 parts of water and is miscible with alcohol. Dose, 4 cc. (U. S. P.), 2 to 8 mil. (B. P.).

Sulphonal, sulphonal ($(CH_3)_2C(SO_2.C_2H_5)_2$), (B. P.) occurs as a colorless, odorless, prismatic, white, crystalline powder soluble in 450 parts of water, 15 parts of boiling water and in 80 parts of alcohol. Dose, 0.3 to 1.2 grams.

Urethanum (B. P.), urethane, $NH_2{:}COOC_2H_5$. Dose, 1 to 2 grams.

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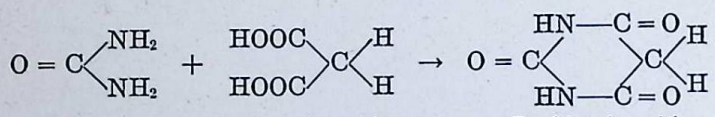
2. Barbituric Acid Group

In 1903, Fischer and von Mering introduced veronal (now known as barbital), diethylbarbituric acid (diethylmalonylurea), as a hypnotic. It has been estimated that more than 1200 homologues of this substance exist; more than 100 have been studied pharmacologically and more than thirty have been recommended for therapeutic use. It may be stated that the chief difference between barbital and the other barbituric acid derivatives is due to a difference in length of action. Alterations in chemical configuration are responsible for the chief differences between barbital and its derivatives. This is reflected in the rate of destruction by the liver and excretion by the kidney, which in turn determines the length of action of each compound. These factors also play a part in the potential toxicity of the various derivatives.

Barbital is related chemically to urea and to hypnotics of the carbamate series. If urea reacts with malonic acid, barbituric acid is formed.



Urea Malonic acid Barbituric acid

When the hydrogen atoms of the end carbon are substituted by ethyl groups, barbital or diethylbarbituric acid results. One or both of the ethyl groups may be replaced by other alkyl, aryl, or complex cyclic radicals leading to the formation of various barbituric acid compounds.

Generally speaking, the hypnotic property of a barbituric acid derivative depends upon the type of substitution in the barbituric acid molecule. Replacement of a hydrogen atom by a phenyl group decreases cortical motor activity; complex cyclic substitutions decrease stability and increase destruction in the body; replacement by long side chain radicals may make the compound exhibit convulsive properties. In addition, barbituric acid compounds possess the ability to form salts which are freely soluble in water, the acid being almost insoluble (*cf.* table on pp. 318, 319 and 320).

The barbiturates are probably misused more than any other group of drugs. This results often from the failure of the physician to familiarize himself with the relative merits and differences in action of the various members of the group and using them indiscriminately.

Pharmacological Action.—The effect on the central nervous system is the most important action of these drugs, and the action is essentially *sedative* and *hypnotic*. More analgesia is produced than with chloral hydrate (especially seconal), but this is not as marked as with drugs of the antipyretic group. The localization of barbiturates in the central nervous system has been demonstrated by numerous studies. Keeser and Keeser found the greatest concentration in the diencephalon—especially in the thalamus—in contrast to the cerebral hemispheres. The former region is of particular significance in the phenomenon of sleep. Barbiturates probably interfere with glucose oxidation in the brain. (Dameshek *et al.*). With usual sedative doses and in the absence

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of pain, sleep is induced in about thirty minutes and lasts from three to five hours. Duration of action and the after-effects depend upon the barbiturate used. Alurate appears to be somewhat cumulative and along with large doses of barbital may cause a slight hangover. As a rule, however, patients awake refreshed and suffer no ill feelings the morning after the drug is taken.

The substitution of one ethyl group in barbital by a phenyl radical makes phenobarbital especially active against increased *motor activity* of the cortex. While all the barbiturates possess anti-convulsant properties when given in large doses, phenobarbital has a selective action and is preferred in epilepsy and other convulsive states.

Depression of a descending nature, similar to that of the general anesthetics, can be produced by large doses of the barbiturates, but the activity of the vital centers is so markedly reduced that only evipal and sodium pentothal should be used for this purpose. (See **Uses**, p. 324.) Amytal administered intramuscularly causes a profound quieting effect on the neuromuscular system as measured in terms of action-potentials (Jacobson).

With ordinary doses, barbiturates affect *reflexes* only slightly. Indeed, the reflexes may be increased in some instances, and it requires large or anesthetic doses of these compounds to eliminate them entirely. Amytal and pentobarbital (nembutal) may occasionally cause excitement in children and old people.

The effect of the barbiturates upon **respiration** is slight when ordinary doses are administered. Toxic doses depress respiration through a direct central effect and depth as well as rate is decreased. When given in conjunction with morphine, barbiturates are additive in their depressant effects upon the respiratory center. Amytal and pernoston appear also to depress respiration through decreased carotid sinus reflexes. Pulmonary edema is not an uncommon occurrence with large doses of the barbiturates of which perhaps amytal is the more frequent cause. Large doses of these compounds seriously impair respiration, and if death occurs, it is due to paralysis of the respiratory center.

The **circulation** is little affected with therapeutic hypnotic doses of the barbiturates. The pulse rate and blood-pressure are slightly decreased as in sleep similar to the effect upon respiration. There is no indication that the myocardium is directly damaged even with large doses, although the vasomotor center is markedly depressed in acute poisoning and peripheral vasodilatation results. Experimentally, Marri and Martinetti found that barbiturates sensitize the carotid sinus to epinephrine, but clinical experience does not bear out this finding. As a matter of fact, Baxter and Robbins report that small doses of amytal prevent cardiac irregularities caused by cyclopropane.

Barbiturates are often used to reduce the tonus of the *gastro-intestinal* tract. This action is not marked but is constant, and the effects are chiefly due to the central hypnotic action of these drugs although Gruber has reported a direct depression of intestinal tone *in vivo*.

The barbiturates produce many **Miscellaneous** effects, but these are of didactic interest only. *Liver function* is not decreased by hypnotic

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COMPARISON OF BARBITURATES

Compound (sodium salt = S)	Chemical name and formula**	Average adult hypnotic dose in grams. Duration of action† (approximate)	Destruction by liver	Per cent excretion by kidney	Special effects
Alurate—S N. N. R.	Allyl-isopropyl $CH_2CH{:}CH_2$, $CH(CH_3)_2$	0.065–0.13 Long	–	20–25	Apt to cause "hangover." Cumulative.
Amytal—S N. N. R.	Ethyl-isoamyl C_2H_5, $CH_2CH_2CH(CH_3)_2$	0.1–0.3 Moderate	+	3–5	Excitement not uncommon. Used prior to anesthesia.
Barbital—S U. S. P., B. P.	Diethyl C_2H_5, C_2H_5	0.3 Long	–	75	Least absolute toxicity. Apt to cause "hangover." Cumulative.
Dial N. N. R.	Diallyl $CH_2CH{:}CH_2$, $CH_2CH{:}CH_2$	0.1–0.3 Moderate to long	±	30	
Evipal—S N. N. R.	Dimethyl-cyclohexenyl CH_3, CH_3, $C{=}CH{-}CH_2{-}CH_2{-}CH_2{-}CH_2$	(See Column 6) Ultra-short	++++	0	For intravenous use 2 to 4 cc. of a 10 per cent solution usually produces anesthesia.
Ipral—S N. N. R.	Ethyl-isopropyl C_2H_5, $CH(CH_3)_2$	0.12–0.25 Moderate to long	±	3–8	Tolerance not so easily developed.

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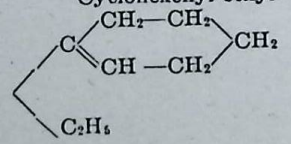
Neonal N. N. R.	n-Butyl-ethyl C_2H_5 $CH_2CH_2CH_2CH_3$	0.05–0.1 Moderate	++	0	Excellent sedation
Nostal N. N. R.	Isopropyl-β-bromallyl $CH(CH_3)_2$ $CH_2CBr:CH_2$	0.1–0.3 Moderate	++	0	
Ortal—S N. N. R.	n-Hexyl-ethyl $CH_2CH_2CH_2CH_2CH_2CH_3$ C_2H_5	0.2–0.4 Moderate	++	0	
Pentobarbital—S U. S. P.	Ethyl-1-methylbutyl C_2H_5 $CH(CH_3)CH_2CH_2CH_3$	0.1–0.2 Short to moderate	++	0	Often used prior to anesthesia. Excitement in old persons not uncommon.
Pentothal—S U. S. P.	Ethyl-1-methylbutyl C_2H_5 $CH(CH_3)CH_2CH_2CH_3$	(See Column 6) Ultra-short	++++	0	For intravenous anesthesia, 2 to 3 cc. of a 5 per cent solution is usually effective.
Pernoston—S N. N. R.	Butyl-β-bromallyl $CH(CH_3)CH_2CH_3$ $CH_2CBr:CH_2$	0.2 Short to moderate	++	0	
Phanodorn N. N. R.	Cyclohexenyl-ethyl 	0.1–0.2 Moderate	+	3 5	Excellent in neurasthenia.

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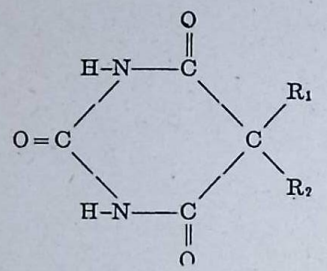
COMPARISON OF BARBITURATES—(*Continued*)

Compound sodium salt = S)	Chemical name and formula*	Average adult hypnotic dose in grams. Duration of action† (approximate)	Destruction by liver	Per cent excretion by kidney	Special effects
Phenobarbital—S U. S. P., B. P.	Ethyl-phenyl C_2H_5 / C_6H_5	0.1–0.2 Long	–	25	Least toxic on basis of efficiency.
Sandoptal N. N. R.	Isobutyl-allyl $CH_2CH(CH_3)_2$ / $CH_2CH{:}CH_2$	0.2 Short	+++	0	
Seconal—S N. N. R.	Allyl-1-methylbutyl $CH_2CH_2{:}CH_2$ / $CH(CH_3)CH_2CH_2CH_3$	0.1–0.2 Short	+++		

* The table shows R_1 and R_2 substitutions only in Column 2. In pentothal, S is substituted for the O attached to C_2.



† Long = 10 to 12 hours; moderate to long = 8 to 10 hours; moderate = 6 to 8 hours; short to moderate = 4 to 6 hours; short = 3 to 4 hours; ultra-short = ½ to 1 hour

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doses, but some of the glycogen stores are depleted when anesthesia is produced by sodium pentothal. The short- and moderate-acting compounds are destroyed in the liver, and the presence of hepatic dysfunction will increase their toxicity.

Ordinary doses of the barbiturates usually cause some *oliguria* followed by polyuria with return to normal in about twelve hours. Larger doses decrease water diuresis and may cause partial anuria if the blood-pressure has been greatly lowered. The long-acting compounds are excreted chiefly by the kidney and hence renal impairment increases the toxicity of this group. The possibility that certain barbiturates may affect the action of diuretics is suggested by the work of Nyary on rabbits. He reported that phenobarbital usually increased the diuretic effect of such substances as caffeine, theophylline, salyrgan, hypertonic sodium sulfate, sodium chloride, and urea. In addition, alurate is said to increase salyrgan diuresis while barbital has no effect on water excretion following the intravenous injection of physiological saline. De Bodo and Prescott found that phenobarbital, amytal, and pentobarbital sodium inhibited water diuresis only if some part of the neurohypophysis was functioning. By contrast, however, phenobarbital even in large doses did not consistently inhibit diuresis produced by isotonic sodium sulfate and isotonic sodium chloride.

The barbiturates produce little if any effect upon *metabolic processes* unless large doses are administered. The *blood chemistry* is somewhat altered by amytal and evipal, the former decreases the pH, causes mild hyperglycemia, and slightly decreases the calcium content. Evipal reduces the oxygen capacity and causes a slight increase in blood sugar. Barbital is said to increase the clotting time of the blood. The *autonomic* effects of the barbiturates vary remarkably. Evipal, pentobarbital, ortal, and amytal antagonize vagal effects while pentothal is said to enhance vagus activity. Pentobarbital and amytal are perhaps more prone to cause *idiosyncric effects*, such as excitement and restlessness. "Hangover" is probably more often seen with the longer acting compounds, such as barbital and alurate. Unlike the atypical effects of morphine, sex appears to play no part in these reactions. With ordinary doses *intracranial pressure* is little affected. Large doses cause some decrease with a usual subsequent increase in spinal fluid pressure if acute poisoning results (Reifenstein and Reifenstein).

Barbiturates are easily **absorbed** from the intestinal tract, from muscle, subcutaneous tissue, and rectum. Hence they may be administered by all routes as above, and in addition, the thio-derivatives are injected intravenously. None of the other compounds should be given by vein, and it is doubtful that they even need to be given by any form of injection. Barbiturates readily pass the placental barrier and are distributed in the fetal tissues. Indiscriminate use of them during labor may markedly depress respiration in the fetus.

Excretion.—As already indicated, long- and moderate-acting barbiturates are excreted chiefly by the kidney. Excretion is not rapid, however, since ten days after a single dose of barbital, traces may be found in the urine. Phenobarbital, alurate, amytal, ipral, and phanodorn are also eliminated by the kidney but to a less extent than barbital. With large doses of any barbiturate, small amounts may spill over and be excreted by the kidney. The short and ultra-short compounds are

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destroyed in the liver in a period of time paralleling their duration of action.

The importance of the kidney in the elimination of barbital is further shown by the fact that experimental animals with severe nephritis never recover from the depression caused by barbital, while similar animals to which are given barbiturates, which are not eliminated by the kidneys, recover from the effects in spite of the kidney condition.

Koppanyi and Dille have shown that rabbits, given daily fractions of the lethal dose and excreting only about one-half of that administered, should theoretically in time store several times the fatal dose in their tissues, and yet they show no severe depression. In contradistinction to rabbits, cats show continuous depression during the period of drug administration and eventually die in barbital coma. The increase in resistance in rabbits is apparently due to an enhancement in the ability of certain tissues, probably the liver, to oxidize the barbital. This destruction is further shown by the fact that only small amounts of the drug are found postmortem in the body. Also the amount which is found in the blood during the course of treatment steadily increases for a time and then begins to decline.

A new classification of barbiturates based on the site of their detoxification has been proposed by Masson and Beland. These authors partially hepatectomized and completely nephrectomized rats and then compared the length of sleep produced by various barbiturates in normal and operated animals. They called the ratio of $\frac{\text{average duration of anesthesia of control animals}}{\text{average duration of anesthesia of operated animals}}$ the "index of intoxication," and the higher the index, the less of a given barbiturate was destroyed by liver or "detoxified" (excreted) by the kidney. (See Table, p. 318.) Finally, they report the unusual finding that pentothal is not destroyed to any extent in the liver or kidney but rather is possibly detoxified in all tissues of the body.

Antagonism and Synergism.—The efficiency of barbituric acid compounds in the treatment of poisoning from cocaine, strychnine, and similarly acting drugs has been demonstrated by numerous workers, both on experimental animals and clinically. Convulsions may be controlled by the intravenous injection of suitable barbiturates, and the lethal dose of strychnine and cocaine in animals may be increased from two to four times by administration of barbituric acid preparations. In certain clinics, these compounds have been used routinely previous to procaine infiltration as a protective measure and to increase the anesthetic effect.

The stimulating effect of caffeine and ephedrine in barbiturate narcosis is generally recognized, and it has been demonstrated that within certain limits the effect of picrotoxin can be neutralized by barbital. Also, Tatum and his co-workers, as well as other observers, have ascribed to picrotoxin a superiority over a number of suggested antidotes in acute barbiturate poisoning.

Barbiturates, while possessing little analgesic power, have the property of increasing the analgesic potency of the salicylates and of amino-

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pyrine. In addition, they significantly reduce the concentration of drugs used to produce general anesthesia. This is especially true when cyclopropane is the agent used. DeNito has reported a potentation of the narcotic action of barbital by acetyl-beta-methylcholine, and Slaughter has shown that neostigmine increases the hypnotic action of barbital, alurate, and pentobarbital.

As regards their **margin of safety**, several of the derivatives of barbital are more actively hypnotic than the parent substance and may be preferred, especially as sedatives. However, there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is significantly wider than in the case of barbital itself. On the basis of a ratio between the effective dose and toxic dose, Adriani lists the margin of safety in order as phenobarbital, barbital, amytal, pentobarbital, dial, neonal, and sandoptal. In any instance, when used properly, the barbiturates possess a low toxicity, but if used indiscriminately, they are dangerous drugs.

Poisoning, Habit Formation and Tolerance.—Much is still to be learned concerning the manifestations of idiosyncrasy and overdosage of the newer compounds, but they do not differ markedly from those of barbital and phenobarbital. In fact, most of the toxic signs and symptoms described in connection with the earlier compounds have been experienced with those more recently introduced.

The importance of poisoning and habit formation becomes very apparent when it is realized that in 1940 more than 1,500,000,000 grams of barbiturate compounds were sold. Furthermore, suicidal deaths for the year 1936 due to barbiturates numbered 300. From 1928 to 1937, one out of every 1900 admissions from thirteen hospitals (total admissions, 1,250,000) suffered from acute barbiturate intoxication, and the fatality rate was 7.3 per cent. Death was most often due to barbital, phenobarbital, and amytal, but this probably indicates only that these drugs were more easily procurable than some of the other compounds. At autopsy, splenic engorgement, pulmonary stasis, and hemorrhages of the cortex have been reported. Amytal and pentobarbital are usually more apt to cause gross and microscopic pathological changes.

Symptoms of **acute** barbiturate poisoning are chiefly those of cerebral and medullary depression, but on occasion, mild convulsions interrupt the stupor and coma before death ensues. The pupils are often pinpoint and morphine poisoning must be ruled out. Skin eruptions sometimes occur, but they are usually not serious in nature. Winer and Baer report a fatal case of exfoliative dermatitis due to phenobarbital; a rare occurrence. Amounts necessary to cause death cannot be accurately stated but fifteen times the ordinary hypnotic dose endangers life.

Richards reports that the toxicity of pentothal and pentobarbital in frogs is increased by lowered temperatures and by hyperthyroid activity caused by thyroxin administration. In mice, adrenalectomy increases the toxic effects of these drugs.

Indiscriminate sale of the barbiturates has not only led to acute poisoning, but of greater economic importance is the increase in habit formation with *tolerance* and *semi-addiction* as the end result. While

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addiction in its strictest sense (appearance of serious symptoms upon withdrawal) may not occur, *habituation* is common. Hambourger has stated that the barbiturates account for one-tenth of all drug habits and that one-third of all patients developed a craving when the drug was withheld. All of the barbituric acid compounds may cause a chronic habit, but amytal and pentobarbital are considered to be most often responsible. Definite tolerance develops to barbiturates but not to the extent seen with morphine addiction.

Nystagmus is present in 66 per cent of cases of chronic poisoning due to the barbiturates and convulsions occur in 10 per cent of all cases. In the mild cases, euphoria is common and mania may be the end result. The Romberg sign is usually positive and motility disturbances are of a cerebellar nature. In contrast to the bromide rash, the cutaneous lesion produced by barbiturates is usually urticarial in nature and is spread diffusely on the trunk and extremities.

In cases of acute poisoning with the hypnotics, the general *treatment* consists in the immediate evacuation of the stomach by the stomach tube. Emetics are of less value owing to the depression of the medullary centers. The patient ought to be kept warm, and analeptics should be given to stimulate respiration. The complete failure of the breathing has to be met by artificial respiration.

The most important consideration in the treatment of acute poisoning is to bring about a return of normal central nervous system activity. The analeptic drugs of choice are caffeine and sodium benzoate, 0.5 gram, ephedrine sulfate 25 mg., picrotoxin 2 mg., or strychnine sulfate 2 mg., all administered parenterally. However, one should not hesitate to repeat or increase these amounts if single doses are not effective in combating the central depression in hypnotic poisoning. It is now recognized that picrotoxin is the most successful antidote if properly employed (*cf.* p. 389). In addition, oxygen is a valuable adjunct, and Reifenstein has proposed the intravenous infusion of 200 cc. of 50 per cent glucose in promoting diuresis and in combating the edema of the brain and lungs.

Sodium succinate has been proposed as an antidote in barbiturate poisoning on the basis that it furnishes an oxidizable substrate until the barbiturate can be destroyed or excreted since its oxidation is not inhibited by barbituric acid derivatives. Experimentally, Pinschmidt *et al.* have shown that sodium succinate is of some value but that it does not compare with moderate doses of picrotoxin.

The treatment of barbiturate habituation consists of the complete withdrawal of the responsible compound. In addition, measures to combat the various symptoms should be instituted.

Therapeutic Uses of Hypnotics.—The hypnotics are chiefly used to produce rest and sleep in cases of insomnia and in almost every form of nervous excitement. The physician should always remember that persons who are emotionally indisposed exhibit similar clinical pictures to those who are merely exhausted. Mild degrees of tension, restlessness, nervous irritability, and insomnia may be treated with hypnotics, but the underlying cause for these conditions should be determined lest con-

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tinued use of sedative drugs result in a habit of dependence. Habit formation may be avoided to a large extent if it is necessary to administer a sedative over a long period of time by alternating various hypnotics one with the other.

Until the discovery of the therapeutic value of chloral, opium was used in most of these cases, and when sleeplessness is due to pain, it is still preferable to the more modern remedies, which have comparatively slight influence on acute pain except in very large doses. However, continued use of the opiates will lead to a habit in most patients and hence their use should be limited because of the chances of addiction. But in delirium, mania, and convulsions of various kinds, their action is preferable to that of opium, especially where these convulsions are of spinal origin or of a reflex nature; thus in strychnine poisoning and in tetanus, chloral, paraldehyde, phenobarbital, and other barbituric acid derivatives are of great value although in strychnine poisoning they may have to be reinforced by chloroform during the convulsions. In delirium from fever or from uremic intoxication and similar causes, comparatively small doses often produce most satisfactory results, and in various spasmodic affections, such as cough, asthma, and choreic movements, hypnotics are exceedingly useful.

Most of the hypnotics have been used more or less extensively in simple insomnia and in insanity, but when the disturbance assumes a more violent character, there is a disposition to return to the use of chloral and paraldehyde as at once the speediest and surest remedies of the whole group. The sedative dose of chloral is 0.2 to 0.7 gram and the hypnotic dose is 0.7 to 1.5 grams. It is best given in a pleasant tasting vehicle, such as syrup of citric acid or elixir glycyrrhiza. The dread of its affecting the heart deleteriously in *ordinary* doses is quite unfounded. Paraldehyde is also a safe and effective hypnotic and would be more widely used if it were not for its objectionable taste and smell and the difficulty of prescribing it. The usual sedative dose is 4 to 6 cc. administered in cracked ice, but larger amounts up to 16 to 20 cc. may be given orally or by rectum for wild delirium. Paraldehyde is of especial value in delirium tremens since it can be administered rectally and acts quickly. Its potential toxic effect, however, should always be kept in mind. Wechsler has recommended the intravenous administration of 1 cc. of paraldehyde for prolonged or rapidly recurring convulsions, and this is probably a useful procedure.

In recent times chloral and older hypnotics have been largely replaced as mild sedatives of the central nervous system by barbital and its allies. The barbiturates are efficient but possess limitations since they are ineffective in severe delirium and high tension states unless they are administered intravenously. For emergency treatment in poisoning due to convulsive drugs and bacterial toxins, sodium amytal and sodium pentobarbital in doses of 0.6 and 0.4 gram respectively may be administered by the intravenous route. The injection must be made very slowly and signs of respiratory depression should be carefully noted. Sedative doses are usually about one-fourth the amount of that used for hypnotic action; for example, 30 mg. of phenobarbital two or three

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times a day is considered a sedative dose while 0.15 mg. may be used to produce hypnosis. The barbiturates are unexcelled for the prevention of toxic reactions caused by local anesthetics, and it is a good plan to administer one of them before the use of cocaine or its allies. The patient with hypertension benefits greatly from sedative doses (usually phenobarbital) given two or three times a day. In this connection, the elixir of phenobarbital is preferred by some clinicians. Nervous tension is allayed, and the patient's mental outlook is improved.

It is not practical to list each individual use of all of the barbiturates nor to suggest which one is preferred. As already stated, the important thing to remember is that the physician should familiarize himself with three or four of these compounds so that he will have confidence in their therapeutic effects. For oral use, barbiturates are administered in capsules, as tablets, or in an elixir.

Phenobarbital possesses a special ability to decrease motor activity of the cortex, and hence it is useful in epilepsy. Ordinarily, 0.1 to 0.13 gram is administered daily. Depending on the circumstances and results, this dose may be increased as much as 0.6 gram per day, but the patient must be closely watched (Lennox). It is of greatest value in the *grand mal* attacks, has some value in psychomotor and focal types of epilepsy, but is not very effective in *petit mal*. One of its chief drawbacks is that large doses stultify the patient's ability because of the inherent hypnotic action it possesses. Continued use of large doses causes ataxia, dizziness, psychosis, and even paranoid symptoms, although many patients have taken 0.065 to 0.13 gram each day for years without apparent harm.

Use in Anesthesia.—In recent years, paraldehyde has been used as a pre-anesthetic hypnotic, and as an analgesic in obstetrics. For pre-anesthetic use, 16 cc. in 120 cc. of milk is administered as a retention enema one hour before the operation. One-half hour before the operation morphine and atropine are given hypodermically. This procedure reduces the amount of general anesthetic needed.

The barbiturates occupy a prominent position as useful drugs for pre-anesthetic medication. Claims that the members of this group cause pulmonary complications resulting from prolonged respiratory depression are unfounded. For pre-anesthetic medication, the preparations with a short duration of action are recommended so that prolonged postoperative effects will be eliminated.

The intravenous use of evipal and pentothal sodium to produce anesthesia has increased since their introduction in 1933 and 1934 respectively (Lucas). Evipal, while popular in England, has not been used in this country as much as pentothal sodium. The discussion of barbiturates in anesthesia will be limited to the latter although the indications for its use and the contraindications and dangers apply to both compounds.

The principal advantages of intravenous pentothal are the ease and pleasantness of induction, absence of the excitement stage, adequate muscular relaxation, and lack of serious postoperative complications. In this latter connection, Fett, *et al.* report an incidence in a series of 500 patients of headache in 10 per

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cent, nausea in 11 per cent, and restlessness in 11.5 per cent. Disadvantages include a relatively narrow margin of safety, variability of response by patients, hiccup and laryngeal spasm if the anesthetic is too light, and disorientation following recovery in the elderly patient.

In practice, morphine and atropine are administered forty-five minutes before pentothal is given. Then 2 to 3 cc. of a 5 per cent solution is injected in about fifteen seconds. The full effect should appear in about thirty-five seconds, and if it does not, then an additional 2 or 3 cc. may be injected. Brooks has pointed out that a 2½ per cent solution is safer, and it is preferred. (For evipal anesthesia 2 to 4 cc. of a 10 per cent solution is recommended.) For longer operations, it may be necessary to administer additional amounts of pentothal, and the usual signs of anesthesia will serve as a guide for the anesthetist to follow. If it is desirable, a nitrous oxide-ether-oxygen mixture may be used following the initial intravenous dose of pentothal sodium. The anesthetist will find that much less of these anesthetic agents are then required to maintain a satisfactory anesthesia.

One can say in conclusion that pentothal sodium is a relatively safe anesthetic if it is administered by a well-trained anesthetist where no contraindications exist. It certainly holds a definite place in the armamentarium of general anesthesia.

Contraindications to the use of barbiturate anesthesia are those of the other general anesthetics, but in addition, it is unwise to use them in persons suffering from any allergic disease.

Preparations

Barbitalum, barbital (U. S. P.), Barbitonum (B. P.), barbitone (diethylbarbituric acid) ($C_8H_{12}N_2O_3$), an odorless, colorless or white crystalline powder with slight bitter taste. One gram dissolves in about 130 cc. of water and 15 cc. of alcohol. Dose, 0.3 gram (U. S. P.), 0.3 to 0.6 gram (B. P.).

Barbitalum Sodicum (U. S. P.), Barbitonum Solubile (B. P.), soluble barbital ($C_8H_{11}N_2O_3Na$), odorless, white powder with a bitter taste. One gram dissolves in about 5 cc. of water and it is only slightly soluble in alcohol. Dose, 0.3 gram (U. S. P.), 0.3 to 0.6 gram (B. P.).

Elixir Phenobarbitali, elixir of phenobarbital (U. S. P.). Each 100 cc. contains not more than 0.43 gram of phenobarbital, absolute alcohol content about 14 per cent. Dose, 4 cc. (One average dose contains 16 mg. of phenobarbital.)

Hexobarbitonum (B. P.), hexabarbitone, hexobarbital ($(CH_3)(C_6H_9)C$:-CO:N:(CH_3):CO:NH:CO), colorless, odorless, tasteless crystals, soluble in about 3000 parts of water. Dose, 0.25 to 0.5 gram.

Hexobarbitonum Solubile (B. P.), soluble hexobarbitone, soluble hexobarbital (B. P.), ($(CH_3)(C_6H_9)C$:CO:$N(CH_3)$:CO:NNa:CO), a white odorless powder with a bitter taste. Very soluble in water and alcohol. Dose, by intravenous or intramuscular injection, 0.2 to 1 gram; by rectal injection 2 to 4 grams.

Phemitonum (B. P.), phemitone, prominal ($(C_2H_5)(C_6H_5)C$:CO:$N(CH_3)$:-CO:NH:CO), a white crystalline powder, odorless and tasteless. It is almost insoluble in water and is soluble (90 per cent) in alcohol. Dose, 0.03 to 0.4 gram.

Pentobarbitalum Sodicum (U. S. P.), Pentobarbitonum Solubile (B. P.), pentobarbital sodium, soluble pentobarbital ($C_{11}H_{17}N_2O_3Na$), white crystalline powder with no odor and a bitter taste. Dose, 0.1 gram (U. S. P.), 0.1 to 0.2 gram (B. P.).

Phenobarbitalum (U. S. P.), Phenobarbitonum (B. P.), phenobarbital ($C_{12}H_{12}N_2O_3$), white, odorless crystals or powder. One gram dissolves in about 1000 cc. of water and in 10 cc. of alcohol. Dose, 30 mg. (U. S. P.), 0.13 to 0.12 gram (B. P.).

Phenobarbitalum Sodicum, phenobarbital sodium (U. S. P.), Phenobarbitonum Solubile, soluble phenobarbitone (B. P.), ($C_{12}H_{11}N_2O_3Na$), flaky crystals, white powder or crystalline granules with no odor and a bitter taste.

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It is very soluble in water and alcohol. Dose, 30 mg. (U. S. P.), 0.03 to 0.12 gram (B. P.).

TABELLÆ BARBITALI (U. S. P.), TABELLÆ BARBITONI (B. P.), barbital tablets. Dose, 0.3 gram (U. S. P.), 0.3 to 0.6 gram (B. P.).

TABELLÆ BARBITALI SODICI (U. S. P.), TABELLÆ BARBITONI SOLUBILIS (B. P.), barbital sodium tablets. Dose, 0.3 gram (U. S. P.), 0.3 to 0.6 gram (B. P.).

TABELLÆ PENTOBARBITALI SODICI, pentobarbital sodium tablets (U. S. P.). Dose, 0.1 gram.

TABELLÆ PHENOBARBITALI (U. S. P.), TABELLÆ PHENOBARBITONI (B. P.), phenobarbital tablets. Dose, 30 mg. (U. S. P.), 0.03 to 0.12 gram (B. P.).

TABELLÆ PHENOBARBITALI SODICI (U. S. P.), TABELLÆ PHENOBARBITONI SOLUBILIS (B. P.), phenobarbital sodium tablets. Dose, 30 mg. (U. S. P.), 0.03 to 0.12 gram (B. P.).

THIOPENTONUM SOLUBILE, soluble thiopentone, pentothal sodium (B. P.), a yellowish-white powder with a bitter taste. Soluble in water and partially soluble in alcohol. Dose, by intravenous injection, 0.1 to 0.3 gram.

In addition the N. N. R. lists the following barbiturates as acceptable to the Council on Pharmacy and Chemistry of the American Medical Association: Alurate, Amytal, Dial, Evipal Sodium, Ipral, Neonal, Nostal, Ortal Sodium, Pentothal Sodium, Pernoston, Phanodorn, Sandoptal, Seconal Sodium, and Vinbarbital Sodium. (See p. 318 for details.)

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IV. OPIUM SERIES

Opium has been used in medicine since a very remote period, and although many substitutes have been proposed for it in late years, it still occupies a very prominent position in therapeutics. Thomas Sydenham's remark made in the seventeenth century, "without opium I would not care to practice medicine" is often quoted. Opium is obtained from the dried juice (latex) of the *Papaver somniferum*, a poppy which is grown chiefly in Bulgaria, Yugoslavia, India, China, Egypt, Persia, and Asia Minor. Most of the opium used for medicinal purposes in this country comes from India, Asia Minor and Persia. It owes its activity to a large number of alkaloids of which *Morphine*, *Codeine*, and *Papaverine* are the most important in decreasing order. *Narcotine*, *Thebaine*, and *Narceine*, while occurring in considerable amounts in opium, are not used clinically.

Other alkaloids in opium include Pseudomorphine, Codamine, Laudanine, Laudanosine, Meconidine, Lanthopine, Cryptopine, Protopine, Papaveramine, Rhœadine, Oxynarcotine, Hydrocotarine, Gnoscopine (or Racemic Narcotine), and Tritopine; many of these occur only in traces. In all, more than 25 alkaloids have been isolated.

The total alkaloids in opium vary from about 5 to 25 per cent, and different specimens may contain very different quantities of each alkaloid; for instance the content of morphine in different samples varies from 2.7 to 22.8 per cent. The average percentage of morphine is 10, of narcotine 6, papaverine 1, codeine 0.5, thebaine 0.3, and narceine 0.2; the others occur in too small quantity to have influence on the action of the crude drug. The alkaloids are found in opium in combination with meconic, lactic, and sulfuric acids.

Chemistry.—The structural formula of morphine is shown on p. 330. The table below indicates chemical differences between it and other important opiates. The position in which a change occurs is noted in the formula of morphine and likewise in the columns below.

Opiate	Position 3	6	7	8
Morphine	OH	OH	H	H
Methylmorphine (codeine)	OCH_3	OH	H	H
Ethylmorphine (dionin)	OC_2H_5	OH	H	H
Dihydromorphinone (dilaudid)	OH	= O	H_2	H_2
Diacetylmorphine (heroin)	CH_3CO	CH_3CO	H	H

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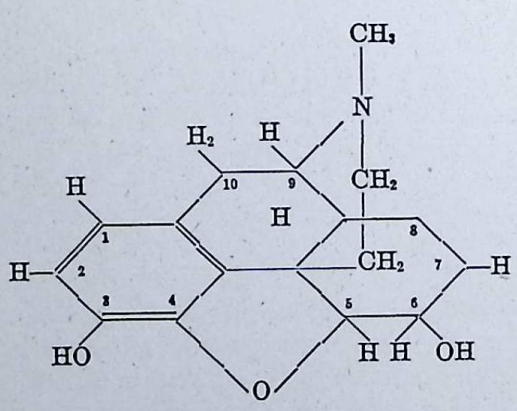
The empirical formula of narcotine is ($C_{22}H_{23}NO_7$) and of thebaine ($C_{19}H_{21}NO_3$). Morphine, codeine, and thebaine are derivatives of phenanthrene ($C_{14}H_{10}$). As shown in the structural formula, morphine contains two OH groups (one phenolic, the other alcoholic). Replacement of the phenolic OH by the methyl radicle (in codeine) decreases the narcotic action and increases respiratory and tetanic effects. With ethylmorphine, narcotic actions are also diminished. Dilaudid differs in that the alcoholic OH has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation. This brief chemical discussion indicates that the innate analgesic and narcotic action of morphine rests chiefly in the phenolic OH since when it is masked, analgesic effects are reduced.

Morphine was isolated in 1803 by Serturner, a drug clerk. He first gave some to dogs and described its narcotic effects and later gave himself and three friends "one-half grain in one-half drachma of water" orally. It is a rather remarkable fact that the amount he used approximates the usual therapeutic dose of today. In 1855, Alexander Wood described the first 10 cases in which from "1/10 to 3/10 grains" of morphine were administered hypodermically.

Papaverine, narcotine, and most of the other alkaloids are related to derivatives of benzyl isoquinoline. As shown on p. 349, the structural formula of papaverine bears no relation to that of morphine. The phenanthrene group of alkaloids differs considerably in action from the isoquinoline derivatives and is diametrically opposed to them in many respects.



Morphine

The action of opium is mainly due to the large amount of morphine contained in it, though the other alkaloids may modify its effects. Hence, the effects of morphine will be discussed in detail and the differences between its actions and those of codeine and papaverine will be pointed out as necessary. Morphine acts chiefly on the central nervous system, but it also affects some peripheral organs, especially the intestine and its action varies considerably in different animals.

Symptoms.—In **Man** small quantities of morphine (8 mg., $\frac{1}{8}$ gr.) lessen the voluntary movements and produce a drowsiness which soon passes into sleep, unless the patient is continually aroused by his surroundings. As long as he is kept awake, his actions and movements show nothing abnormal, but it is impossible to keep his attention directed to any object for long, and as soon as he is left to himself for a few

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moments he sinks into sleep. After small quantities there is no difficulty in arousing him; in fact, the sleep seems lighter than usual and may resemble rather a state of abstraction or "brown study." In this condition (euphoria) the imagination is not depressed to the same extent as the reason; the self-control and judgment are lessened, and although the stream of thought may seem more rapid and the images more vivid than usual, the logical sequence and the ideas of time and space are lost, and the condition may rather be compared to dreaming than to a real increase of the intellectual powers. Even in this early stage pain is felt less acutely, the respiration is slow, and the pupil contracted.

In larger quantities (15 to 30 mg., $\frac{1}{4}$ to $\frac{1}{2}$ gr.) morphine produces deep, dreamless sleep, from which the patient is still easily aroused, but to which he returns at once when he is left undisturbed. When once aroused, he can be kept awake or can be aroused again after a short interval much more easily, some time apparently elapsing before the same degree of depression is reached. As the dose is increased, the sleep deepens into torpor, from which he can be awakened only with difficulty, and eventually all efforts to arouse his attention are fruitless and he sinks into coma, which may be reached very soon after a large dose. During this deeper sleep and coma the respiration is very slow, the pulse is regular, full, and of moderate speed. The pupils are contracted to a small point and the mouth and throat are dry. The face is purple and congested, and the skin feels warm, although the temperature may be low. The breathing generally becomes slower and weaker, and occasionally periodic (Cheyne-Stokes). The cyanosis increases, the pulse becomes smaller and often quicker, the pupils remain contracted, but dilate widely just before the final arrest of the respiration. The heart continues to beat feebly for a short time afterwards.

After small doses of morphine the patient generally awakes refreshed, and save for occasional dryness of the throat and slight nausea, is apparently quite normal. Not infrequently, however, headache is complained of, and sometimes nausea and vomiting, accompanied by marked depression. In rare cases delirium, and even convulsions, have been observed soon after its injection, but these symptoms of excitement are so rare in the human subject as to be classed as idiosyncrasies. Some skin affections, such as itching and redness, are occasionally seen while the action is passing off.

Action.—The action of morphine on the **Central Nervous System** in man is mainly depressant, but it differs from the alcohol-chloroform group in its selective action on the respiration and on pain sensation, which are both much reduced by doses which have little effect on the general consciousness. As already indicated, euphoria is often an outstanding effect of morphine although it is not always experienced by all individuals. It does occur with great frequency, however, and the sense of well-being experienced by most patients is largely responsible for habit formation after repeated administrations. The most constant effect of morphine is its analgesic action; the ability to relieve pain. Even though the discomfort of pain is entirely removed, the intelligence is almost as acute as usual, and the patient is able to answer questions

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and converse freely. He may seem also to be unusually sensitive to impressions caused by loud noises or sudden flashes of light. While constant pain is alleviated, a sudden jabbing pain is not as easily allayed and when the patient is once aroused, the sensitiveness to pain apparently persists for some time. Morphine thus seems to lessen the power of attention, and under it the individual remains almost unconscious of any constant stimulus, but he can be aroused by a sudden intense stimulus and only relapses to his former lethargy after some time. Seevers and Pfeiffer showed an interesting inverse relationship between the narcosis and analgesia produced by morphine. Using humans as experimental subjects, they noted that while the peak of analgesia was reached in sixty to ninety minutes after a subcutaneous injection of 8 mg. of morphine that narcosis and depression was greatest after the pain threshold had returned to a normal level.

Many methods to measure pain threshold responses produced by morphine have been devised and none are perfect. Wolff, *et al.* made use of light-heat radiation and tested pain threshold effects of morphine on the blackened foreheads of humans. They found that the subcutaneous injection of an average therapeutic dose of morphine (15 mg.) would raise the pain threshold about 70 per cent. Their work was based on the finding that all patients have the same normal pain threshold; a suggestion not compatible with clinical experience or the work of Chapman or Slaughter and Wright. Using an improved technique and comparable doses, the latter authors did not find such a marked increase in pain threshold as did Wolff, *et al.*

Attempts to localize accurately the site of the narcotic and analgesic effect of morphine or to explain its mechanism of action have not yielded clear-cut results. Analgesic action is predominantly central, and the electroencephalographic experiments on humans reported by Berger, Gibbs, *et al.*, and Andrews are indicative of cortical depression. Bernheim and Bernheim and Slaughter and co-workers have suggested that morphine may act centrally through a cholinergic mechanism. The former authors demonstrated that rabbit brain esterase was inhibited by morphine while the latter investigators have reported in animals and in man that neostigmine, which potentiates acetylcholine activity, enhances the analgesic action of morphine. Hardy and Wolff had previously shown that epinephrine reduced the pain threshold-raising property of morphine and had concluded that "this action . . . was due to a change in the central pain mechanism which made it refractory to the . . . action of morphine." This view fits the central cholinergic postulate although Goetzl, *et al.* have reported that dextro-amphetamine enhances the analgesic action of morphine in mice.

The observations of Wolff, *et al.* that the analgesic action of morphine and of codeine is reduced by the presence of pain is contradictory to its clinical use for pain relief. These authors explain this discrepancy by stating that the opiates partially impede the perception of pain but of more importance, they detach the perception of pain from the "fight-flight-anxiety" so closely attached to it. In other words, the patient recognizes the pain, but doesn't care about it. Further objective experiments are needed in order to clarify these statements.

Codeine possesses about one-fifth the analgesic potency of morphine and causes much less euphoria. On the other hand, when given in ordinary amounts, *papaverine* exhibits little, if any, analgesic action.

The opiates have little direct effect on auditory, olfactory, visual,

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muscular, or *cutaneous sensations;* a decrease in pain and temperature effect on the latter being the chief exception. It has been reported that mental processes are temporarily facilitated by small doses of morphine, but such an effect can be explained away on the basis of euphoria.

The *motor areas* of the cerebral cortex are not affected by small doses of morphine, but larger quantities lower and eventually abolish the excitability to electric shocks. Experimental reports that morphine is a synergist with central convulsants or is a convulsant drug itself are speculative and unproven. Although experimentally morphine has been shown to possess anticonvulsant properties, its effectiveness in man is doubtful. Even though it has been used in the treatment of epilepsy, eclampsia, etc., other agents were used with it and hence proof of its anticonvulsant effects is difficult. If convulsions do occur, they are seen most frequently in children—this may be a philogenetic indication of preponderance of spinal cord activity in the young with greater cerebral control coming into play in later life.

The action of morphine on the *medullary centers* resolves itself into a discussion of the separate functions of this area. It can only be stated that the most pronounced effect is seen upon the center controlling respiration.

The effect of morphine on the central nervous system has often been referred to as biphasic (depression and stimulation) in character. Its action on *reflexes* is not clear, but it is generally agreed that spinal cord activity is heightened by morphine in some instances, and hence is not the drug of choice in the treatment of poisoning by strychnine. *Codeine,* on the other hand, usually increases spinal cord reflexes, especially if more than 64 mg. is given at one time, while *papaverine* seems to have no effect.

In animals, the central nervous symptoms of morphine present an extraordinary mixture of stimulation and depression and the relative prominence of these varies widely in different species. The stimulation of the brain is best manifested in the wild excitement of the cat and its allies under morphine, while the narcotic action predominates in the rabbit and to a less extent in the dog; even in the cat some depression of the intelligence is to be made out. In the cat and rabbit the respiration is depressed as in man, but in the dog there is a stage of marked acceleration present at first. In the dog the vomiting center is primarily excited, but this stage of stimulation is followed by one of depression. If very large doses of morphine are given to dogs, the depression of the center comes on almost immediately, vomiting being entirely absent. The cardiac inhibitory center of the medulla is also stimulated, although the action on the vagus center is said to be largely an indirect one from an action upon the cortex. It is impossible at present to suggest any general theory of the action of morphine on the nerve cells which covers these differences in the behavior of different animals and also in the reaction of different nerve centers in the same animal. In animals, symptoms of excitation produced by codeine are more obvious, especially in the spinal cord, in which the reflexes are rendered more acute and may finally give rise to spasms. In the cat, morphine induces cerebral excitement, but under codeine this is often seen in the dog also and even to a slight extent in man. In the frog, the evidences of a stimulant action are more marked with codeine than with morphine.

Hambourger has shown that morphine produces excitation in the cat even after bilateral cerebral decortication. He suggests that the subcortical centers must, therefore, play a rôle in this phenomenon. It should be emphasized that

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even though morphine does cause wild excitation in the cat, definite analgesia is also produced. Finally, amphetamine antagonizes the cortical and respiratory depression produced by morphine (Handley and Abreu, and Goetzl, *et al.*).

To sum up the action of morphine on the central nervous system: it produces great depression which is especially marked on the perception of pain and on the respiration; the imagination and the cerebral motor functions are less affected than the power of perception, the will, and the attention. In man the failure of the respiration closes the course of the intoxication, but in the cold-blooded animals a further development of excessive reflex irritability follows, which may pass into tonic convulsions. Even in the higher animals and man some indication of this action of the cord may occur, and in the feline group this stimulation involves not only the cord, but also the motor areas of the brain.

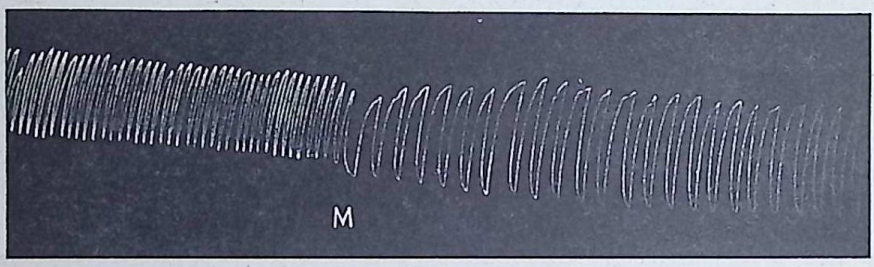

FIG. 23.—Respiration of the cat. At *M*, injection of morphine intravenously. The respiration is immediately slowed and the movement is increased in depth.

Respiration.—In man and in most other animals the respiration is slowed and the minute volume is decreased by morphine from the beginning (Fig. 23), and as the dose is inc eased, the slowing becomes progressively greater. After small quantities which have no other appreciable effect, the breathing may be rather shallower, but as the rate slows the depth increases, though not sufficiently to compensate for the slowing, and the total air breathed may fall to one-half the normal or less. The characteristic effect of morphine is thus a diminution in the rhythm of the center, which remains susceptible to reflex stimulation, but is unable to accelerate the discharge of impulses to the same extent as normally. The inhalation of carbon dioxide in unpoisoned animals quickens and deepens the respiration, but under morphine, while it deepens it as much as before, it is unable to quicken it in the same measure. If morphine causes rest and sleep, less carbon dioxide is formed in the tissues, and though less is excreted owing to the slowness of the breathing, there may be no accumulation in the blood and the depth of the respiration remains unchanged or may be shallower. But if the slowing is more marked, the gas accumulates in the blood and acting on the respiratory center, it deepens the breathing, as it cannot accelerate it except to a limited extent.

Dripps and Comroe found that an intravenous dose of 10 to 20 mg. morphine produced maximal depressant effect in three to seven minutes, but the effects were not significantly greater than with intramuscular injection. Respiratory minute volume, rate, and tidal exchange were

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diminished and respiratory effort was diminished in 4 of 26 patients studied, and in no case was any appreciable increase in depth of respiration noted. These authors suggest that the beneficial effects of morphine in the treatment of clinical dyspnea may be related to a feeling on the part of the patient that breathing simply becomes easier.

In the later stages of morphine poisoning, the breathing often becomes irregular, and this irregularity may have a periodic character, a series of deep respirations being followed by several progressively weaker ones and then by complete inactivity for several seconds. The breathing then recommences with a very slight movement, followed by a series increasing regularly in strength and then again decreasing (Fig. 24).

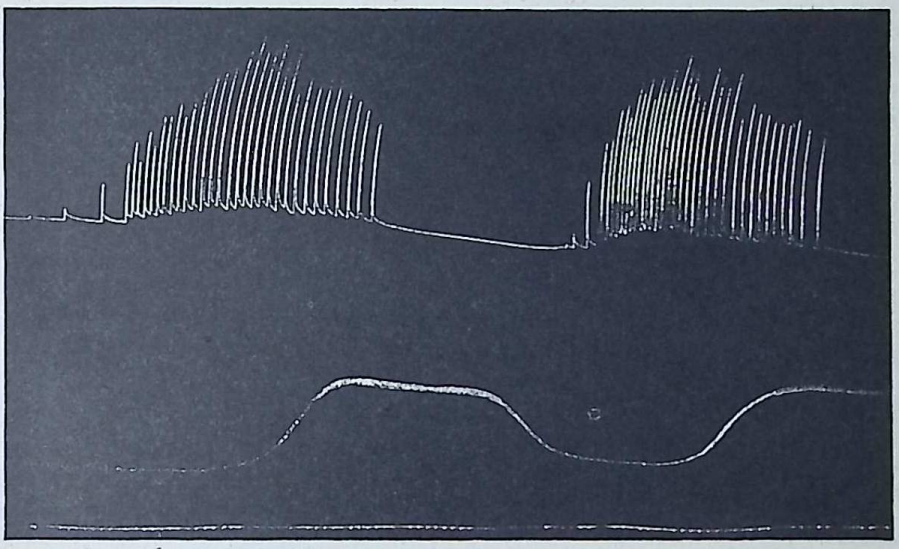

FIG. 24.—Tracings of the respiration (upper) and blood-pressure (lower) during Cheyne-Stokes respiration in a cat under a large dose of morphine. (Barbour.)

This form of respiration (Cheyne-Stokes) appears to arise in part from the depression of the respiratory center, in part from the asphyxia which results from the inefficient respiration. When the respiratory center is once aroused by the accumulation of carbon dioxide and by the anemia, it remains less narcotized for some time and thus a series of respirations follow which reduce the carbon dioxide of the blood and also relieve the asphyxia. The blood supply to the brain increases, and thus the stimuli to the respiratory center furnished by the carbon dioxide and the anemia are both removed and the center again becomes dormant (Fig. 24) until the carbon dioxide again arouses it to a new phase of activity.

Towards the end, the respiration becomes gradually slower and weaker, and often loses its periodic character. Even after consciousness fails to be aroused by the most powerful shocks, some influence may be exerted on the respiratory center. Thus the sudden application of cold water may cause several deep respirations, although it fails to dispel

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the stupor, but the respiration finally fails to react to these applications and soon afterwards ceases.

Jackson has noticed that morphine and many of the other alkaloids of opium constrict the bronchi in animals; this appears to arise from a direct action on the bronchial muscle. Such effects in man, if they occur, would seem to be of no practical significance.

Codeine acts similarly on the respiration as does morphine, but it is only about one-fourth as potent in comparable doses. Both opiates depress the cough reflex, but codeine is superior in this capacity, since cerebral centers are less affected. Heroin is said to be more efficient than either morphine or codeine, but no proof of this has been given.

Morphine has little direct action on the **Circulation** in man; the heart is often slightly accelerated at first, perhaps from the slight nausea. However, most investigators have been impressed with "clinical" slowing of the heart rate, but quantitative experiments have not yielded sufficient evidence that therapeutic doses materially alter the pulse rate.

The blood-pressure remains high and the peripheral arteries in general show no change of caliber, with the exception of those of the skin, especially of the head and neck, which are dilated, rendering the face flushed and hot. As asphyxia come on, the flush becomes more dusky and cyanotic, but the vessels remain dilated so that the face is of a bloated, purple color. The dilatation of these vessels, which is probably due to a dilator effect on capillaries, has little influence on the general pressure, but causes a sense of warmth in the skin, which is occasionally followed by itching and discomfort. It may account in part for the increased perspiration often observed, although this is doubtless contributed to by other factors. As asphyxia advances, the pulse may become slow, while the blood-pressure varies, either rising from the asphyxial activity of the vasomotor center or falling from the slowness of the heart. These effects may be entirely absent if the blood is sufficiently aerated by artificial respiration and are perhaps to be regarded as indirect results of the action on the respiratory center. Morphine does dilate the coronary arteries and relieves dyspnea of cardiac origin. These actions will be discussed more fully on page 352.

Experimentally in most animals morphine depresses cardiac muscle, decreases cardiac output through slowing, stimulates the vagus center, facilitates cardiac reflexes from the carotid sinus, and usually increases cerebral blood flow. In addition, vasomotor responses to sensory stimuli are usually decreased.

The selective action of morphine is well illustrated in its effects on the medulla oblongata in man, for the respiratory center is paralyzed before the cardiac centers are affected to any marked extent. In summary, it may be stated that sufficient doses may cause a depression of the heart rate and vasomotor reflexes, but the only constant effect in man, with ordinary doses, is peripheral vasodilation. Finally, morphine does exhibit a tachyphylactic effect upon the blood-pressure of animals when injected intravenously.

The intravenous injection of morphine in dogs and cats is followed by a marked fall in blood-pressure, which is most pronounced in the primary injec-

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tion and which may be entirely absent in later injections. The fall in pressure may be due in part to a depressant action upon the vasomotor center but it is mainly due to a dilatation of the vessels of the skin and muscles brought about by a direct action of the drug upon the vessel walls. Tolerant dogs do not react to the intravenous injections in the same manner, there being a high degree of resistance to the depressant action of the drug. The disappearance of the reaction upon the later injections of morphine in normal dogs is due to the rapid development of resistance in the vasodilator mechanism, a condition comparable to that seen in the tolerant dogs described above. In rabbits, guinea-pigs, and rats no fall in pressure occurs when morphine is injected (Schmidt and Livingston). These authors have shown that neither the central nervous system, respiratory or cardio-inhibitory centers, vasomotor center, nor cardiac rate significantly contribute to the depressor effect of morphine. They are of the opinion that the main effect is due to a histamine-like dilating action upon the capillaries but physostigmine enhances the depressor effect of morphine in the cat which would indicate that a cholinergic mechanism may be involved.

The effect of morphine on the *blood* is of only minor importance except in addiction where Williams has reported blood hydration. During withdrawal the hydration temporarily decreased and a true concentration did not occur. There is no agreement as to whether single doses alter the number, size, and shape of erythrocytes and no consistent change in hemoglobin has been reported. On the other hand, single doses may cause a leucocytosis and the differential count is similar to that seen in acute infections. Finally, the sedimentation rate in humans is often increased as much as 50 per cent following the administration of therapeutic doses (Schoen).

Codeine possesses no important circulatory effects. Any action noted is similar but weaker than that of morphine. Papaverine, however, is said to have a direct depressant action on blood-vessel musculature, and in addition it raises the fibrillation threshold of the ventricle in experimental animals.

The peripheral **Muscles** and **Nerves** are also unaffected by morphine in any except overwhelming doses. Even when directly applied to the nerve it has but little effect on the irritability. The sensibility of the skin is lowered by an injection, it is true, but this is due to the central action almost entirely. As a matter of fact, paresthesia and itching is not uncommon, and even mild urticaria may develop after a hypodermic injection.

Morphine is prone to cause *vomiting* by directly stimulating the vomiting center. Clinically, this effect is much more common than is usually thought since nausea and/or vomiting occurs in about 8 to 10 per cent of all patients. As soon as the narcotic effect of morphine has taken place, morphine exhibits an anti-emetic action; ordinary emetics are then not capable of causing vomiting.

In morphine poisoning in man, the **Pupil** is contracted to pin point dimensions until just before the final asphyxia, when it dilates widely. While a satisfactory explanation for pupillary differences in animals is not forthcoming, in man the mechanism of pupillary constriction long obscure, has been elucidated by McCrae, *et al.* Their work shows that pupillary constriction caused by morphine is potentiated by neostigmine through an action on the oculomotor nerve, thus indicating that mor-

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phine acts cholinergically. In some animals, such as the dog and rabbit, the same effects are seen, while in birds the pupil remains unaffected, and in animals in which morphine causes movement and excitement, it is dilated widely. In addition, atropine applied to the conjunctiva at once removes the miosis produced by morphine. The terminal dilatation seen in man is not due to any direct action of the poison, but is a result of the general asphyxia.

As a general rule the **Secretory Glands** seem to be rendered less active than usual by morphine. When it produces nausea it may increase the saliva and the mucus, but these are the usual accompaniments of this condition and cannot be considered due to any special action. The sweat glands are exceptions to the general rule, however, for slight perspiration is generally observed from the therapeutic action and perfuse perspiration from the effects of the asphyxia is seen before death in some cases in man. The urine does not generally show any distinct alteration after morphine in man, but there is, not infrequently, retention in the bladder because the sphincter is powerfully contracted.

The anal sphincter is similarly contracted in some animals, and in the mouse this leads to a curious stiffening of the tail, which was at one time considered a specific test for morphine. However, it has now been shown to be induced by many other poisons (Straub test).

The actions of opiates upon the **Alimentary Canal** are complex and the mechanisms involved are not completely understood. This is unfortunate, since constipation, the most outstanding side-effect of morphine, ranks in importance with its respiratory actions and is often more troublesome to the clinician. In the human subject its injection is sometimes followed by some nausea, which is much more frequently present, however, during recovery from the drug. In the dog, nausea and vomiting are almost invariable sequelæ of its application in any form, and seem to be due to its acting on the medullary center. Small quantities of opium or morphine lessen the sensation of hunger in the human subject, but this is probably to be attributed to central action rather than to any effect on the stomach.

The effect of morphine on gastro-intestinal secretions has not been studied sufficiently and further experiments to substantiate its action are desirable. It is generally agreed that salivary secretion is increased, while gastric, pancreatic, and bile secretion are decreased.

Since constipation is the most consistent effect produced by the opiates, the actions of them on the motility and tonus of the stomach, small and large intestine, and upon the defecation reflex are of greatest importance. These effects have been most closely examined in the dog, and for the most part such findings are applicable to man. To Magnus belongs the credit for reporting the first conclusive experiments concerning the effects of morphine on the stomach. Pioneer work in more modern times on all gastro-intestinal effects was done by Plant and Miller. Later, Krueger and co-workers, Yonkman, Gruber, Ivy, Quigley, Veach, and many others have contributed other data which helps explain the complexities of this entire problem.

It is now generally accepted that the chief effects of morphine on the *stomach* consist in decreased tonus and motility with a concomitant contraction of the pyloric antrum and of the pylorus itself. This action

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causes the food to be withheld from its passage into the small intestine, and, coupled with decreased digestion in the stomach (due to diminished gastric secretion), the delay in emptying time constitutes the beginning of morphine constipation. Veach has argued that morphine is predominantly motor to the human stomach, but confirmation of his work has not been reported, and it is difficult to reconcile this effect with the administration of morphine for gastric hemorrhage. Slaughter, *et al.* have shown that in the dog, neostigmine enhances the action of morphine on the stomach, which is another indication of cholinergic activity of this opiate.

The old idea that morphine quiets intestinal movements is no longer considered correct. As a matter of fact, Plant and Miller, in 1926, showed that the chief actions in the *small bowel* were an increased tonus and a decrease in peristalsis. This effect has amply been confirmed in man and in dogs by Forster and Quigley, *et al.* These workers reported that morphine resulted in a decreased propulsion (decreased peristaltic activity) but an increased motor activity (heightened tonus). Since emptying time of the stomach is delayed and less food is poured into the intestine at any one time and since the material in the intestine remains for a protracted period, absorption of water is more complete, resulting in drier contents of the lumen. In addition, the reduction in pancreatic and bile secretion decreases digestive processes in the small bowel. Hence, these effects are additive to those on the stomach in the production of constipation. Neostigmine will enhance morphine effects on the intestine as well as on the stomach.

The *large intestine* responds similarly but to a less degree than the small bowel. Peristaltic and propulsive activity is reduced; tonus is increased and more complete absorption occurs (Jackman and Bargen). These actions contribute to the constipating effect of morphine. The decrease in the defecation reflex and contraction of the anal sphincter further enhance the constipative effects of the drug. In addition, depression of attention to stimuli, induced by morphine, also plays an important rôle in this connection.

The mechanism of the gastro-intestinal effects have not been clearly demonstrated. Increasing evidence suggests that most of the actions may be based on cholinergic manifestations. This seems especially true since denervation and neostigmine enhance the actions of morphine, and atropine in proper dosages will counteract gastro-intestinal effects. It has been suggested that a central mechanism may play a rôle since intraventricular injections of physostigmine potentiate the action of very small doses of morphine on the small intestine. Finally, much work remains to be done before concise statements can be made regarding the pharmacological action of morphine on the gastro-intestinal tract.

Codeine has a less effect than does morphine on the gastro-intestinal tract, but large doses will produce constipation (Fig. 25). Papaverine possesses only a weak antispasmodic effect on the musculature of the gastro-intestinal tract, an action which is of little therapeutic value.

The antidiarrheal action of opium would then seem to depend most largely upon the increase in tone in both small and large intestines,

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which, in addition to delaying the progress of the intestinal contents toward the lower bowel, would also lessen the tendency to local distention of the gut (which in itself is a potent stimulus to powerful peristaltic waves) which would hasten the contents on toward the rectum. Heroin acts much like morphine, but it produces less nausea and vomiting and its constipating actions on the gastro-intestinal tract are probably about one and one-half times more potent.

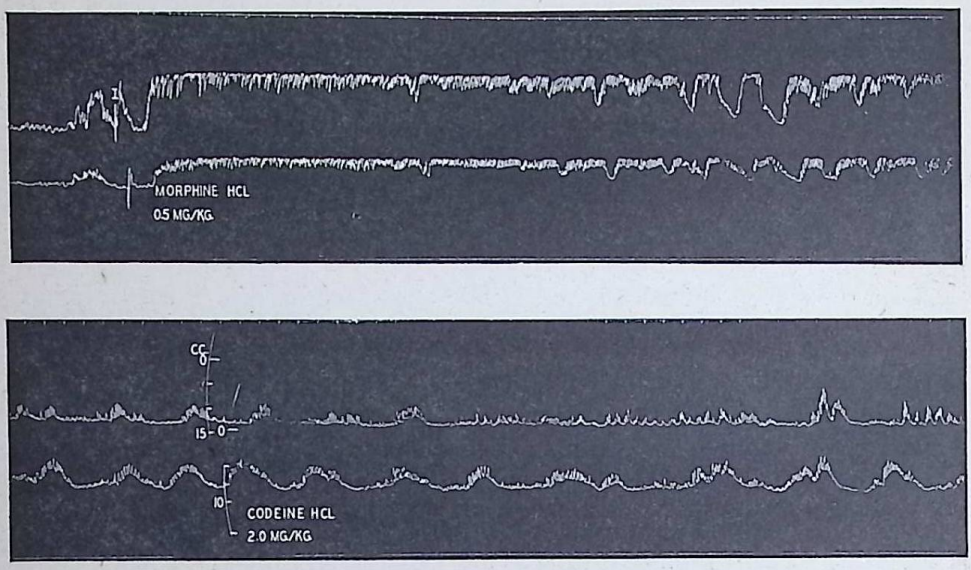

FIG. 25.—Tracings showing comparative effects of morphine and codeine upon the small intestine of an unanesthetized dog. Each pair of tracings was taken from two balloons which were placed in a Thiry-Vella loop of the lower ileum. The upper tracing of each pair was taken from the anterior balloon, the lower in each instance from the posterior balloon. There was no open connection between the balloons. Each was connected to a Brody bellows recorder. The lower pair of tracings (codeine) show the calibration of the capacity of the balloons. The morphine tracings show the increase in tone and in strength of contractions of the intestine which result from the injection of 0.5 mg. per kilogram of body weight of morphine hydrochloride, while the lower pair of tracings show the almost complete lack of effect from a dose four times as great of codeine (2 mg. per kilogram). The tracings were taken on different days so that lack of effect in the case of codeine is not due to the previous administration of the morphine. (Krueger.)

In animals many forms of **Unstriated Muscle**, such as intestine, ureter, uterus, bronchial muscle, and bladder, have been shown to be aroused to increased contraction and tone under the influence of morphine and the other phenanthrene alkaloids, while the isoquinoline derivatives depress their activity; after repeated injections the contractions from the phenanthrene group fail to occur, while the organ continues to respond to various other poisons. It is unknown whether the action is exerted on the muscle directly or on the peripheral nervous structure.

By means of hydrophorographic tracings, Ockerblad, *et al.* studied the effect of morphine on the human *ureter* and found that the tonus and amplitude of contractions were consistently increased. Furthermore, morphine stimulates the *biliary* tract in man since pressures of the common duct are markedly increased after a therapeutic dose. Careful studies by Van Duzen *et al.* and Winter reveal that in the dog morphine

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causes an increase in the tonicity of the detrusor muscle, a fall in urethral resistance, and a marked decrease in bladder capacity. They attribute these effects to be due to a peripheral cholinergic action of morphine. The effects of morphine on the *uterus* are not well-defined and need further investigation. Using a manometric method, Bourne and Burn found that morphine prolonged and decreased the frequency of contraction and delayed relaxation of the parturient human uterus. Falls, *et al.* found that morphine inhibited the frequency but augmented actual contractility. In the non-parturient uterus of unanesthetized dogs, morphine acts similarly to that described by Bourne and Burn.

The reported effects of morphine on **Metabolism** are so numerous, complex, and contradictory that any attempt to discuss them fully would be futile. (For details, the reader is referred to the United States Public Health Service publication, Supplement No. 165, pages 247 to 413.) It is generally agreed that morphine causes hyperglycemia in animals by increasing the liberation of epinephrine. In man this has no practical significance. Reducing substances do appear in the urine after therapeutic doses. Oberst has suggested that glucuronic acid is the chief reducing compound, but complete evidence has not yet been produced. Morphine forms compounds with and modifies the properties of proteins. Loofs suggested that morphine replaced choline in the lecithin molecule and many workers have shown that morphine depresses the choline esterase of blood and tissues both *in vivo* and *in vitro*. Clear-cut evidence of morphine effects on nitrogen metabolism are not forthcoming, but disturbances of the nitrogen economy are produced. With regard to mineral metabolism, most reports indicate a temporary, slight decrease in blood calcium and phosphate after therapeutic injections. In experimental animals, tubular resorption of water seems to be increased. Oliguria is the usual response of diabetic patients to morphine, while diuresis has been noted in cardiac patients receiving digitalis.

In man, therapeutic doses usually decrease the *basal metabolic rate* about 8 to 10 per cent during the first hour; presumably the action is one of central nervous system depression. In addicted dogs, the basal metabolism is increased and during withdrawal, a similar effect due to restlessness and muscle twitching is often noted.

Therapeutic doses of morphine cause little change in body *temperature*. Larger amounts produce some fall due to lessened activity, heat dissipation from peripheral vasodilatation and central depression of the heat-regulating mechanism.

After single doses, morphine decreases oxygen consumption about 10 to 15 per cent and increases the alveolar carbon dioxide tension about 2 to 3 mm. Blood carbon dioxide remains normal. Response to carbon dioxide in the inspired air is usually decreased and the blood may shift as much as 0.05 pH to the acid side.

Oxygen consumption of rat brain decreases in the presence of glucose, but no difference in this effect between tolerant and non-tolerant animals was noted (Gross and Pierce). *In vitro* experiments by Bernheim and Bernheim indicate that rat liver slices oxidize morphine at the OH groups. The reaction did not occur anaerobically or after boiling the slices. "Dilaudid" is also oxidized under these same conditions, but codeine and "dionin" inhibit the oxidation of morphine.

Absorption and Excretion.—Morphine is readily absorbed when given orally or by parenteral injection. Some is even absorbed when rubbed

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onto broken skin surfaces, and the sublingual administration is highly effective.

The kidney comprises the chief route of excretion of morphine, only a small amount being excreted in the feces. Traces are said to be found in the saliva, sweat, and milk, but no conclusive evidence has been offered to show that a nursing baby is affected if the mother is administered morphine. Plant and co-workers were first to prove conclusively that in the dog most of the morphine was excreted by kidney rather than by bowel. However, they were only able to account for about one-fifth of any given dose and likewise excretion studies in man gave similar figures. To Gross and Thompson goes the credit of showing that most all of administered morphine may be recovered in the urine of dogs. They hydrolyzed and autoclaved urine containing morphine and found that the total excretion in non-tolerant animals amounted to 80 to 92 per cent while for tolerant animals the figure was about 45 per cent. The "*free*" morphine analyzed by old methods amounted to only about 10 per cent of the total while the other 90 per cent was composed of the "*combined*" morphine which had been hydrolyzed by acid and heat. However, tolerant and non-tolerant dogs excreted about the same amount of the "free" form, the reduction in the total excretion by tolerant animals being reflected in a lessened elimination of the "combined" form. It is obvious, therefore, that a low percentage excretion of "combined" morphine is a special characteristic of tolerance. Thompson and Gross have also shown that the "combined" form of morphine contains two fractions—an easily hydrolyzable and a difficultly hydrolyzable form. When the latter type is analyzed, it is found that the non-tolerant animal excretes a total of 94 per cent of a given dose and a tolerant dog eliminates 65 per cent. What happens to the rest of the morphine is at present unknown; it may or may not be destroyed. Liver damage increases the excretion of "free" morphine, but has little effect on total excretion. These results may suggest that some morphine is conjugated in the liver but the recent report of Bernheim and Bernheim (p. 341) casts considerable doubt on this possibility.

Oberst has reported similar findings in human subjects but the "free" and "combined" amounts were about one-half that recovered from dogs; in addicts, 5 and 30 per cent respectively. He did note that the fractional amount of "bound" morphine increased over the "free" portion at higher dose levels. By contrast, Slaughter, *et al.* showed that neostigmine decreased the excretion of both forms of morphine in the dog, but the greatest reduction was reflected in the "combined" form. If the hypothesis, as suggested by Gross, that the "combined form" is responsible for analgesia is true, then the reduction in excretion of it might help explain the potentiation of morphine analgesia by neostigmine. In addition, Oberst's report that high dose levels increased the excretion of the "bound" form might indicate that complete tolerance depends to some extent on the maintenance of a "just sufficient" amount of "combined" morphine. Fecal excretion accounts for about 5 per cent of the total amount eliminated, all being in the "free" form.

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About 75 per cent of codeine is recoverable from the urine but the fate of papaverine in the body is unknown.

Acute Poisoning with morphine or opium is said to be one of the commonest forms of intoxication. However, statistical data does not bear out this concept since probably not more than 1000 authentic cases have been recorded. Fortunately also, death from acute poisoning is not common; the average number of persons dying from this cause being roughly 60 per year. It is often difficult to diagnose. The extreme contraction of the pupils gives a clue, as a general rule, but it must be remembered that large doses of the barbiturates also contract this organ, but if opium has been used, the breath often has the characteristic odor. The symptoms produced by toxic doses of the opiates are reflected in a profound central nervous system depression. The therapeutic actions of sleep, decreased respiration, and relief of pain are markedly increased. Deep coma is the rule in adults, but in children this may be preceded by convulsive seizures. The blood-pressure and pulse may be only moderately decreased until the final stage of asphyxia sets in. Spontaneous emesis is not common, general opinion notwithstanding. Perspiration is not uncommon, and even in the terminal stage, a cold, pale, clammy skin is often noted. As the respiration fails, cyanosis is pronounced and death is due to paralysis of the respiratory center. Some observers (Schmidt) in particular have stated that circulatory failure plays a dominant rôle in death due to opium poisoning, but more confirmative evidence is needed on this point. Animal experiments indicate that morphine is more toxic early in life (Gibbs and Bobb and Eddy). However, studies on humans do not bear out completely this contention, with the exception that infants under four months are more susceptible. On a weight basis, those above four months are scarcely more sensitive than adults. In summary, a Cheyne-Stokes type of respiration (p. 335), deep coma, pin point pupils with asphyxial dilatation before death, and cyanosis are signs of acute opium poisoning. The elapsed time between the administration of opium and a fatal outcome is said to be from three to twelve hours. Because of the variation of response to morphine in acute poisoning, exact fatal doses may not be stated. However, 2 to 5 grams of opium (dried) and 0.25 to 0.5 gram of morphine will probably cause death in most adults. At autopsy, the findings are chiefly those of asphyxia, but pulmonary edema is commonly noted also.

The **treatment** of acute morphine or opium poisoning should consist in removing the poison from the body and in guarding against failure of the respiration. The first object is best attained by washing out the stomach with the stomach tube, as emetics generally fail when morphine has been absorbed, owing to the depression of the center. In addition, the depressant after-effects of these drugs may be detrimental, When morphine has been injected hypodermically, gastric lavage is of little, if any, value. Water should be used to wash out the stomach since dilute potassium permanganate solution tends to oxidize the gastric mucous membrane rather than the morphine.

Besides increasing the excitability of the respiratory center by these drugs, the normal stimulus may be augmented. Thus respiration may be

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aroused reflexly from the skin by dashing cold water on it, or by the electric current, or by flicking it with wet cloths. But the chief normal stimulus of the respiratory center is the carbon dioxide of the blood, and an attempt should be made to increase this and thus to promote the aeration. This may be attained by keeping the patient in motion as far as is possible, in order that the muscles may supply CO_2, but as this may have to be done for several hours, it entails great fatigue both for patient and attendant. A more rational method of enriching the blood with CO_2 would be to allow the patient to breathe air containing 7 to 10 per cent of the gas, which might be kept in readiness in the hospitals where opium poisoning is often encountered.

Finally, if the respiration fails in spite of these measures, artificial respiration must be employed and continued as long as the heart beats. Cases of recovery from enormous doses of morphine are recorded in which artificial respiration was maintained for many hours.

A patient should be kept warm to prevent loss of heat from the dilated peripheral blood-vessels. After recovery, a cathartic may be administered to counteract the obstinate constipation which usually occurs. The symptoms of acute codeine poisoning are similar to those seen with morphine, although convulsions more often occur in adults. The treatment is also essentially the same. Death due to codeine has not been reported.

Tolerance and Addiction.—A good deal of confusion exists regarding the usage of these words and hence certain definitions are given below:

1. "*Tolerance* is a phenomenon characterized by the fact that more and more of a drug must be used to produce equivalent effects.
2. "*Addiction* is that condition of mind or body induced by drugging which requires a continuation of that drug, and without which a serious physical or mental derangement results.
3. "*Habituation* means a condition wherein one becomes accustomed to but not seriously dependent upon a drug." (Tatum, Seevers, and Collins.)

In addition, Himmelsbach adds the term "*dependence*" as denoting a "distortion of normal physiologic process" resulting from prolonged administration of opiates to the extent that the body requires them in order to maintain a physical as well as psychical equilibrium. Dependence is the essential feature of addiction, and it should not be confused with habituation. Finally, tolerance always develops before addiction so that it is not possible to demonstrate dependence before tolerance is developed.

The continued use of morphine or opium in man leads to a condition of tolerance, in which enormous doses of the drug are necessary to elicit their usual effects. As a general rule, daily therapeutic administration of morphine will cause tolerance in about three weeks. Tolerance develops more rapidly if the dose is increased, hence no more than the least amount per day which will relieve pain should ever be given.

In some animals a similar condition of tolerance has also been attained by the repeated administration of morphine and in monkeys this condition has apparently been best developed. After these animals receive the drug for several

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months they show a marked dependence upon it, and if the drug is stopped tolerance is lost in about two weeks.

Dogs can also be rapidly rendered tolerant if large doses of morphine are given, while if small doses are used the process is a slow one. In cats and certain other animals, a moderate degree of tolerance is also said to have been gained.

The mechanism by which the body gains its resistance to the large doses of morphine is not understood in spite of many laborious researches which have been carried out on the subject. Many theories have been advanced to explain the phenomenon of morphine tolerance but none have been proven. However, the evidence points to some change in the cells of the nervous system. Finally recent excretion experiments (p. 342) indicate that a low percentage excretion of "bound" morphine is characteristic of tolerance.

The inability of morphine to relieve pain after repeated administration is a common clinical observation. Hence, tolerance to the narcotic action of morphine not only is most striking but occurs before other evidences of tolerance are noted. In addition, morphine early fails to depress respiration, and this effect almost parallels the ease of tolerance developed for pain relief. Furthermore, tolerance is developed for acute toxicity, emetic action and probably for vagal slowing of the heart. No tolerance is developed in man for the effects of morphine on the intestine, pupil, or local skin reaction following a hypodermic injection.

Tolerance to the toxic effect of morphine is lost in two or three days unless addiction is present and even then it disappears as soon as the abstinence symptoms have subsided. Many so-called cured addicts have died as a result of taking at the end of their withdrawal period a dose to which they were accustomed during addiction.

Animal experiments have shown similar tolerance manifestations, thus dogs which have become so tolerant that even large amounts fail to induce narcosis, continue to react even to small quantities by slowing of the pulse. The cerebral nerve cells have become tolerant, as have also the cells of the respiratory center, the vomiting center, and the nervous mechanism controlling the pupil; but the cells of the vagus center have failed to do so. The bowel also continues to react to morphine as in the beginning, but the emptying time of the stomach decreases indicating development of tolerance for this organ (Harned and Curl). Some nerve cells thus become habituated to the presence of morphine in the blood while others remain susceptible. Dogs which have been rendered tolerant to morphine are also refractory to its allies, codeine and heroin.

Tolerance for codeine is difficult to develop in animals. In fact, patients may appear more susceptible to the drug after several doses, and a dose which at first gave relief now causes nausea and vomiting. It is possible that this may indicate a tolerance of some parts of the central nervous system which is not shared by the vomiting center. However, humans addicted to morphine have been satisfactorily maintained for a week or two on adequate doses of codeine, indicating that a cross tolerance for this drug can be developed during addiction. Tolerance to papaverine has not been proven.

Chronic Opium or Morphine Poisoning (Addiction) is not an infrequent condition, but seems to be decreasing somewhat. Among eastern nations, especially China, opium is smoked (Chandoe) and some of

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the morphine is carried over in the smoke and absorbed from the respiratory tract. This habit is rare in other parts of the world where the drug is taken by mouth, generally in the form of the tincture of opium (laudanum) or powdered opium pills, or is injected hypodermically as morphine hydrochloride or sulfate.

The opium habit began with the use of opium in medicine, but addiction to morphine developed only after the introduction of the hypodermic needle by Wood in 1855. Addiction to opium by smoking or eating the crude drug does not significantly differ from the addiction produced from repeated hypodermic injections of morphine.

It is difficult to determine the actual number of opium and morphine addicts but the latest estimates give a figure of about 120,000 in the United States, 800 in Great Britain, and about 8,000 in Canada. In Europe and Asia, information on this point is extremely meager. It will indeed be interesting to obtain reports as to the effect of World War II on this important problem.

In the beginning the quantity used is small, but as tolerance is attained, ever larger quantities are required to produce any effect, until as DeQuincey states in his "Confessions of an Opium-Eater," "320 grains of opium may be required to stay the craving." Amounts taken daily by morphine addicts vary greatly but an average dose for the usual addict is about 100 to 200 mg.

If an addict is able to obtain a sufficient amount of morphine at regular intervals which will prevent withdrawal symptoms, it is difficult to denote any change in physiological behavior. As a matter of fact, careful tests on more than 500 addicts indicate only slight variations from the normal. Of some importance may be the findings of mild anemia, and a uniformly high blood lactic acid. Emaciation was noted only in those addicts who could not afford a proper diet or who lived under unhygienic surroundings. In addition, constipation and digestive disturbances are not uncommon and a psychology develops whereby every act of living is motivated chiefly by a need to maintain a sufficient intake of the drug (Light, *et al*).

Opinions differ widely as to the mental deterioration present in opiate addiction. Unless the patient was psychotic before the addiction, it is doubtful if any definite changes occur. It is true that most experienced addicts soon evince a desire for continuation of the drug and craving is considered to be as pathognomonic of addiction as is the abstinence syndrome. There is, however, a reduction in efficiency of an addict when results of various psychological and psychophysiological tests are compared before and after dependence is established.

Autopsy findings in human addicts are not specific. Congestion in various organs and fatty infiltration in others have been reported. Reports in rats suggest a regular incidence of giant cells in the spleen, but normal controls also exhibited this finding. It may be stated categorically that there is no pathology of morphine addiction except the addiction itself.

Once addiction to morphine is fully developed, the addict not only continues to take the drug because of a craving for it, but also because

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of the fear of withdrawal symptoms. Earlier writers suggested that these symptoms were chiefly psychical and could be controlled by the patient. That such is not true is evidenced by the fact that animals (dog and chimpanzee, especially) exhibit many of the withdrawal symptoms seen in man. It must, therefore, be considered that these symptoms are real and not imaginary although the patient may be able to voluntarily affect a quantitative differential in severity if he is certain that he will or will not receive the drug during the height of withdrawal.

Upon withdrawal of the drug there is a striking change in the condition of the individual due to the appearance of the so-called withdrawal symptoms. These begin with restlessness and yawning. In a few hours the patient complains of being cold, the respiration is jerky, there is difficulty in breathing through the nose and the nasal secretion is excessive. A prolonged sleep may follow but the earlier symptoms recur with increased violence upon awakening. The patient complains of abdominal cramps and vomiting and diarrhea may appear. Sweating is excessive. Muscular twitching is marked. Food and water are refused and sleep is difficult. Physical violence may be threatened. The severity of these symptoms increases up to about the third day and subsides in about ten days, but if at any time during this period the addict should be given his usual injection, his whole appearance and attitude will change and within a few minutes he will be comfortable and in less than an hour will be apparently well and strong.

A quantitative scheme of abstinence symptoms has been worked out by Himmelsbach in order to evaluate various forms of treatment.

ABSTINENCE SYNDROME

Mild	*Moderate*
Yawning	Tremor
Lacrimation	Gooseflesh
Rhinorrhea	Anorexia
Perspiration	Mydriasis
Marked	*Severe*
Rise in temperature	Vomiting
Increase in respiratory rate	Diarrhea
Increase in systolic blood-pressure	Weight loss
Restlessness	
Insomnia	

While the signs given above do not encompass all the symptoms seen during withdrawal, they probably represent those of greatest importance.

Collapse may follow upon sudden withdrawal of morphine from an addict, but death rarely occurs. Mild collapse symptoms are common and of little importance. A most striking laboratory finding during abstinence is a marked leucocytosis which is similar to that seen in an acute infection. In dogs the blood sugar is elevated during the first week of withdrawal and a similar early finding is also seen in man.

The *treatment* of chronic morphine poisoning is not too promising. The will and self control would seem completely paralyzed in many cases, and although the patient may wish to be freed from his enemy, he seems utterly unable to withstand the craving; thus treatment be-

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comes a matter chiefly of rehabilitation. The only means of treatment which promises success in most cases is the strict régime of an asylum or retreat, where the patient is kept under constant supervision. In the withdrawal of the drug resulting in the distressing symptoms already mentioned there are two methods of treatment available. In the one case the narcotic is withdrawn at once, while in the other method the drug is reduced in amount from day to day until none is being administered. Each method has its advocates. The withdrawal symptoms are more severe when the drug is withdrawn abruptly but after the third day they usually begin to decrease in intensity and by the end of a week or ten days the patient is usually comfortable. In the "tapering" process the symptoms are less severe but more prolonged.

It should be emphasized that no drug therapy has been found to be satisfactory in the treatment of opiate addiction. Prolonged use of hypnotics only lengthens the period of craving. Intravenous glucose during the height of withdrawal has been found helpful chiefly in maintaining a somewhat near normal nutritional and metabolic balance. Addicts should not be considered as prisoners, but rather as patients who are mentally ill. Only in this way will adjustment toward a healthy life occur. Of 4,766 male patients treated at the United States Public Health Hospital at Lexington, Kentucky from 1936 to 1940, a check-up three years later revealed that 74.7 per cent of those not dead or unknown had relapsed while 25.3 per cent had remained abstinent. This study emphasizes the fact that the general belief that an addict can never be cured is not true.

As a cause of a drug habit, codeine is of relatively little importance; very few cases of addiction to it have been reported. However, the statement which is sometimes made that codeine has no addicting properties is not strictly correct. Cases of addiction to codeine which have been described are usually not primary addiction but are more commonly secondary to the use of morphine. That is, the patient has become addicted to morphine and when for some reason he is unable to secure this drug he resorts to codeine.

Other Opiates.—Heroin, diacetylmorphine, is a synthetic alkaloid formed from morphine. It resembles morphine in its general effects, but acts more strongly on both cerebrum and medulla than does morphine, and is therefore more poisonous, the usual dose being about one-fourth that of morphine. The action on the respiration is the same in kind as that of morphine, and the advantages claimed for heroin by its advocates have not been confirmed by impartial investigation. It is as effective, but not more so than is morphine, in the treatment of cough, but is less effective in the treatment of dyspnea. Heroin is excreted mainly in the urine unchanged, but some is found in the stools.

Many cases of heroin habit have occurred and this aspect of the drug's action has brought it into serious disrepute. The fact that it can be easily administered and that its dose is small makes trafficking with it easier than with some of the other narcotics. The social danger from it, moreover, seems to be greater than with morphine in that it produces a change in the personality as shown by an utter disregard for the conventions and morals of civilization. Degenerative changes in the individual progress faster than with any of the other narcotic drugs, and all the higher faculties of the mind, such as judgment, self-control, and attention, are weakened and the addict rapidly becomes a mental and moral degenerate. The heroin habit is most difficult to cure, not only in the

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active withdrawal period but also in the convalescent stage, and relapse is frequent. Because of its marked ability to produce habit formation, it is no longer included in the U. S. P. Also, its importation into the United States is illegal.

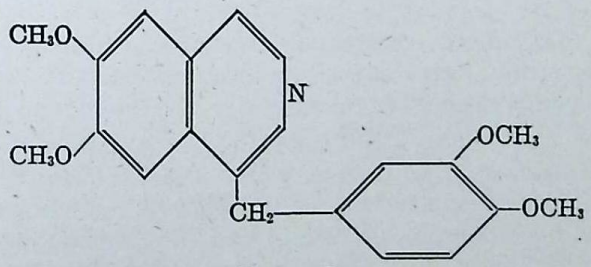
Dihydromorphinone Hydrochloride (Dilaudid) was first described in 1923 and after a brief study was introduced into the clinic, the first report of its action in man appearing in 1926.

Chemically it differs from morphine in that the alcoholic hydroxyl group of that alkaloid is replaced by ketonic oxygen and the adjacent double bond is removed by hydrogenation. The earlier experimental work showed that dilaudid produced analgesia and narcosis and acted upon the respiration in a manner similar to morphine, with the difference that it was effective in about one-quarter the dosage. In the dog, restlessness and vomiting were followed by depression, somnolence, analgesia, and slowing of the respiration. In the rabbit, the respiration was slowed very markedly, but some deepening of the respiration took place so that the effect of the slowing was partially compensated.

The resemblance of dilaudid to morphine which has been shown in the laboratory is confirmed in the clinic. In man the drug is powerfully analgesic and also markedly depressing to the respiration while nausea, vomiting, and constipation are not so marked as with morphine. Tolerance and addiction to dilaudid occurs, as a number of dilaudid addicts have been reported, showing that the same care should be exercised in prescribing dilaudid as is used in the case of the natural opium alkaloids.

Dilaudid is used in the same manner as morphine for the relief of pain and as an analgesic but in much smaller doses—usually 1 to 2 mg. For cough a dose about half that size is used. In general, the dose of dilaudid to be given is about one-fifth that of morphine.

Thebaine seems to have practically no depressant action. It sometimes produces some heaviness and confusion in man, but this is accompanied by symptoms resembling exactly those described under strychnine, and it may, therefore, be considered as belonging to the latter series rather than to that of morphine. It is much less active than strychnine, however.



Papaverine

Papaverine stands midway between codeine and morphine in its action on the central nervous system and is a comparatively weak poison although it does possess a definite, though slight, local anesthetic action. Even in large quantities, it has not the soporific action of morphine, nor does it produce sleep, but on the contrary, the reflex excitability is augmented, and after very large quantities some tetanic

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spasm may be elicited. This seems to be of spinal origin entirely while that produced by codeine points rather to an affection of the lower part of the brain. Papaverine has a greater tendency to slow the heart rate than morphine, and it apparently acts directly on the heart muscle to produce this effect. In addition, it depresses the smooth muscles of arterioles so that when it is perfused through them, the blood-pressure is somewhat lowered. However, ordinary amounts administered systematically cause little if any change. In the dog, papaverine significantly raises the fibrillation threshold of the ventricle when administered in therapeutic doses. Large doses lower the threshold for fibrillation especially if enough is given to cause a sharp drop in blood-pressure. However, there is no conclusive proof that papaverine will bring about spontaneous recovery in a fibrillating heart (Wégria and Nickerson). Its action upon the intestinal tract of the intact animal is practically without therapeutic importance. Upon excised tissues (ureter, gall bladder, etc.) papaverine and the other benzyl isoquinoline alkaloids relax the tone, slow the contractions, and thus antagonize morphine, and it has been shown that this action on these organs and upon unstriated muscle occurs to some extent in man. Papaverine seems to undergo complete destruction in the tissues. Tolerance and addiction to papaverine is unknown.

Ethylmorphine (Dionin) stands about midway between morphine and codeine in its pharmacological effects. However, it is not used for the relief of pain, because it possesses local irritating properties on mucous membranes.

Dihydroisocodeine, Dihydrohydroxycodeinone (eucodal), **Dihydrocodeine** (paracodin), and **Dihydrocodeinone** (dicodide) have all been suggested as substitutes for codeine in the treatment of cough. Of these, the latter, as *dihydrocodeinone bitartrate* (hycodan), deserves special mention. It is less toxic than codeine and possesses less convulsant and emetic activity; also less tolerance is usually noted. For intractable cough in children following infectious diseases, and in tuberculosis in the adult, oral doses of 1 and 5 mg. respectively in a pleasant tasting syrup are efficient.

More than 120 other compounds related to morphine have been synthesized, but only two deserve special mention. The first of these is **Methyldihydromorphinone** (*metopon*). It has no especial advantage over morphine, except possibly in severe chronic pain and in terminal cancer (Lee). It produces tolerance less rapidly than morphine and dependence is lost more easily once established. A comparable analgesia produced by 10 mg. of morphine can be obtained with only one-half as much metopon. The second compound, **6-monoacetylmorphine** not only is about four times more analgesic than morphine, but it appears to permit increased voluntary muscular effort and greater coöperation of mobilization in patients suffering from traumatizing wounds. However, it causes more euphoria than does morphine and hence is probably not suitable for ordinary relief of pain because of its greater addiction liability.

Opium itself contains, besides the alkaloids already discussed, various

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acids with which they are in combination: meconic, lactic, and sulfuric acid, but none of these possess any action of importance. Along with these are found gums, sugars, albumins, wax, and the other common constituents of plant juices, but these merely tend to delay the absorption of the active constituent, and cannot be said to play any part in the effects of opium. Of the alkaloids, morphine is present in greatest abundance, and is also the most powerful in its effects on man. According to most observers, the action of opium on the brain is practically identical with that of morphine, when due allowance is made for the slower absorption of the crude drug from the bowel; if any difference exists, it is so small as to be inappreciable in ordinary cases. However, some clinicians feel that a mixture of all the alkaloids of opium, **Pantopon (Omnopon)**, is less apt to cause nausea, vomiting, and other untoward symptoms as compared with morphine. This has not been shown to have more narcotic action than the morphine that it contains. Being free from extractives it may be given hypodermically in doses of from 0.005 to 0.02 gram.

Therapeutic Uses.—The alkaloids of opium constitute one of the most important and most extensively used group of drugs in the pharmacopeias of the present day as in the past. The crude drug has been largely replaced by its alkaloids, but the action is essentially the same, and although morphine is preferable in most cases, opium is still especially indicated for certain purposes. In almost any disease, conditions which are favorably influenced by morphine may present themselves, and these conditions alone can be discussed here.

As has been repeatedly mentioned, opium or morphine has a special **analgesic** action which is not shared by its modern rivals of the methane series. The general statement may suffice that severe pain indicates opium. Even where the disease itself is one which would, in ordinary circumstances, contraindicate it, it must always be taken into consideration whether the relief of the pain and its attendant restlessness may not counterbalance the disadvantages of the narcotic. At the same time, the danger of inducing the craving for morphine cannot be forgotten, for the use of morphine to subdue pain has been a fruitful cause of the habit. It is often found that comparatively small quantities of opium are sufficient to remove or, at any rate, to dull pain; but after repeated doses the quantity has to be increased owing to tolerance being attained. Codeine may be used instead of morphine to allay pain, but has to be given in at least four times as large a dose, and is ineffective in severe pain. Some forms of pain are relieved by the members of the antipyrine series, but these are less certain and more limited in their action than morphine. On the other hand, the antipyretics will often relieve pains of a neuralgic type and thus they possess a great advantage over opium in the treatment of headache, neuralgia, and similar conditions on account of the elimination of the danger of forming a morphine habit.

The usual hypodermic dose of morphine sulfate is 8 to 16 mg., of "dilaudid," 1 to 2 mg., and of codeine, 30 to 60 mg. However, sublingual administration is highly effective when it is not possible to inject these drugs. Papaverine possesses no analgesic action *per se*. It

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should be emphasized that no two persons exhibit the same degree and intensity of pain and hence doses necessary to relieve pain vary. In any case the dictum "pain is the best antidote for morphine" should always be remembered.

It is not practical to list all the diseases causing pain for which the opiates are indicated. Suffice it to say that the physician must use considered judgment in using these drugs and never administer them thoughtlessly.

The use of opium alkaloids routinely to produce **sleep** should not be condoned, because of the liability of habit formation. If sleeplessness exists because of severe pain, then morphine is indicated. Opium is less efficient than certain of the hypnotics when there is apparently an increased activity of the motor functions of the brain, as in wild delirium and mania, and sometimes seems even to increase the excitement, but this general statement is subject to numerous exceptions, and morphine is still used occasionally in such disorders. In the true convulsive diseases, such as tetanus, epilepsy, and chorea, the chloral group or one of the barbituric acid derivatives is preferable. In certain forms of motor excitation, especially in insanity, scopolamine or a barbiturate may be indicated as a sedative, and in cases of sleeplessness from anxiety and worry one of the barbiturates or potassium bromide is generally preferred to any of the more powerful sedatives. The beneficial effect of morphine in many acute febrile conditions is undeniable, and, as in the case of alcohol, is due to its lessening the pain and discomfort of the patient and inducing rest.

In **Respiratory Disorders** opium and morphine or, perhaps still better, codeine are largely used for their effects on the center. Where it is desirable to lessen its irritability as, for example, in excessive cough and dyspnea, opium may be indicated. On the other hand, when there is a profuse expectoration, the irritability of the center cannot be lowered without danger, and opium is contraindicated. Opium gives relief in cases of asthma, but there is always danger of inducing the habit. In the rapid, shallow breathing of heart disease, the administration of opium or morphine is often followed by slow, deep, peaceful respiration without any reduction in the efficiency of the ventilation.

Opium is often combined with expectorants in the treatment of cough, and a number of suitable preparations are provided in the pharmacopeias, such as Camphorated Tincture of Opium (paregoric) and Powder of Ipecac and Opium, N. F. (Dover's powder), in doses of 4 cc. and 0.3 gram respectively. In addition, the N. F. preparation of Elixir of Terpin Hydrate and Codeine in doses of 4 cc. is a useful preparation for cough. The object of combining expectorants with opium is to allay excessive coughing; the opium reduces the excitability of the center, while the expectorant causes a secretion of mucus in the respiratory passages and thus protects the irritated mucous membrane. The combination is indicated only in dry cough with little expectoration, and when there is abundant sputum to be removed by coughing, the treatment might be unnecessary and even harmful. Codeine is usually preferred to morphine in these cases because it reduces the excitability

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of the respiratory center with less marked cerebral depression. Davenport found that, in the great majority of tuberculous patients requiring medication for the relief of cough, codeine in a dose of 10 mg. orally was sufficient. Ernst found a high degree of potentiation of morphine by codeine in subduing the cough reflex, and recommended a combination of them as superior to either alone. Heroin and dionin were introduced as superior to codeine for relieving cough, but impartial investigators of these drugs have generally failed to obtain better results from them than from codeine and morphine. Of more recent interest is the use of "hycodan," which possesses certain advantages over codeine in the treatment of cough (p. 350).

In **Peritonitis and Intestinal Disorders** opium is indicated doubly; first, for its general action in allaying pain and restlessess; and secondly, for its special action upon the movements of the intestine. Opium is usually considered preferable to morphine for these purposes. In colic, especially lead colic, morphine often relieves the pain without increasing the constipation and seems to allay the spasm of the bowel without stopping entirely its peristalsis. In diarrhea, opium may be given to check the excessive peristalsis, though in the severer forms of dysentery it generally fails to have this effect, and in septic purging is to be avoided. In perforation and hemorrhage from the bowel, opium is the most efficient of all remedies, as it allows adhesions or clots to be formed which would prevent further leakage and at the same time it allays the anxiety and restlessness of the patient.

The pharmacopeias offer a number of preparations especially designed for use in intestinal disorders and especially in diarrhea, such as paregoric, laudanum, or the compound chalk powder.

In **Hemorrhage** where the bleeding point cannot be reached, opium or morphine is most valuable. This is not from any direct effect on the vessels or blood, but because it allays the restlessness of the patient which follows the loss of large quantities of blood, and thus allows the blood to clot in the ruptured vessel. The same preparations are suitable here as for pain.

Morphine in doses of 10 mg., or combined with atropine or scopolamine (0.4 mg.), is frequently given hypodermically as a preliminary to general **Anesthesia**. If a barbiturate precedes this combination, anxiety and apprehension of the patient is allayed and less anesthetic is required. Morphine and scopolamine have been used also to a certain extent in labor ("twilight sleep") but some believe that it is dangerous to the child through depressing the respiratory center and through prolongation of labor. Used judiciously, it affords some analgesia and produces a temporary amnesia which is beneficial to the obstetric patient.

Opium has been used as a **Diaphoretic**, and for this purpose it is generally combined with ipecac and prescribed as Dover's powder. Although in itself it has little or no diaphoretic action, opium may augment the effects of ipecac through dilating the skin vessels. Papaverine and codeine ("copavin"), in 16 mg. doses respectively, have been recommended for the abortion of the common cold. Proof is lacking for

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any specific effect on the disease, but the patient usually feels better—hence they do no harm. Opium and its alkaloids have almost no effect when applied to the skin, and the plaster, ointment, and other similar preparations are obsolete.

Morphine or dilaudid are especially indicated in the treatment of **coronary occlusion** to control the excruciating pain of this disease. Larger doses than usual are often necessary and 8 mg. of morphine may be given *intravenously*. In cardiac dyspnea, morphine is very effective since it makes for a better air exchange by restoring the carbon dioxide pressure of the body and the medulla to a more nearly normal level. The gastric crisis seen in neurosyphilis often demands swift relief of pain and opium alkaloids are often indicated. In shock, where pain and restlessness are severe, morphine is definitely indicated. However, large doses (30 mg.) should not be repeated more often than every six hours unless marked pain is still present or unless the period of shock is well passed. If such a plan is not followed, over-dosage is very apt to occur due to the lessened circulation produced by the shock itself. For the relief of postoperative pain, morphine, combined with neostigmine, has been found to be effective and the dose of morphine required is considerably less than usual. In the pain of terminal carcinoma, opiates must be used cautiously so that tolerance is not too quickly developed. Neuhof's method of giving intravenously 100 cc. of physiological saline containing 4 mg. of morphine per hour may be found useful. Even though morphine increases the contractility of the gall bladder and ureter, it is still used for the pain of biliary and ureteral colic. Its use here is one in which the patient ignores the pain because of its action on the central nervous system.

Codeine is perhaps less often used than morphine in therapeutics as it is of less value than morphine in allaying pain, but it is used very extensively as a sedative in cough and there is little tendency to form the codeine habit.

Because of its general depressant effect on smooth muscle, papaverine (30 to 60 mg. hypodermically or intravenously) is recommended in peripheral embolism, acute myocardial infarction, angina pectoris, mesenteric embolism, bronchial asthma, and renal and biliary colic. In addition, it is probably of value in reducing the tendency toward cardiac arrhythmias. However, two recent reports of death following intravenous injections of 30 to 65 mg. of this drug should serve as a warning that papaverine must be used cautiously when administered by this route.

"Dilaudid" may be substituted for morphine wherever the latter is indicated and pantopon likewise; some clinicians prefer pantopon because they feel that it produces less side effects than does morphine. Opium and its alkaloids must be used cautiously in children, although when the dosage is figured on a weight basis, infants over four months of age are not more susceptible. Meningitis, severe head injuries and acute cerebral congestion are definite contraindications to the use of these drugs. Their use prior to cyclopropane anesthesia is somewhat questionable as it may increase the possibility of cardiac irregularities. In

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addition, use of them is contra-indicated if the patient is not actually suffering from severe pain and if other less habit-forming drugs will suffice.

At the present time, ethyl morphine (Dionine) is employed extensively to produce vasodilatation and edema of the conjunctiva. The chemosis is of value for its analgesic and curative effects in corneal ulcer and other inflammatory conditions in the eye. For this purpose it is usually employed in a 5 to 10 per cent solution, although a 20 per cent solution or even the dry powder is sometimes used.

Preparations

U. S. P.

Æthylmorphinæ Hydrochloridum, ethylmorphine hydrochloride ($C_{19}H_{23}O_3N.HCl.2H_2O$) ("Dionin"), occurs as a white or faintly yellow powder with no odor. One gram dissolves in 10 cc. of water and in 25 cc. of alcohol. Dose, 15 mg.

Codeina, codeine ($C_{18}H_{21}O_3N.H_2O$), occurs as a white crystalline powder, 1 gram being soluble in 120 cc. of water and in 2 cc. of alcohol. Dose, 30 mg.

Codeinæ Phosphas, codeine phosphate ($C_{18}H_{21}O_3N.H_3PO_4.1\frac{1}{2}H_2O$), occurs as a fine white crystalline powder with no odor. One gram dissolves in 2.5 cc. of water and in 325 cc. of alcohol. Dose, 30 mg.

Codeinæ Sulphas, codeine sulfate ($(C_{18}H_{21}O_3N)_2.H_2SO_4.5H_2O$), occurs as white needle-like crystals or powder. One gram is soluble in 30 cc. of water and in 1280 cc. of alcohol. Dose, 30 mg.

Dihydromorphinoni Hydrochloridum, dihydromorphinone hydrochloride, ($C_{17}H_{19}O_3N.HCl$) ("Dilaudid"), occurs as a fine white odorless crystalline powder. One gram dissolves in about 3 cc. of water and it is sparingly soluble in alcohol. Dose, 2 mg.

Morphinæ Sulfas, morphine sulfate ($(C_{17}H_{19}O_3N)_2.H_2SO_4.5H_2O$), occurs as white feathery silky crystals or as white crystalline powder. One gram dissolves in 16 cc. of water and 570 cc. of alcohol. Dose, 10 mg.

Opium, opium, yields not less than 9.5 per cent of morphine.

Opium Granulatum, granulated opium, yields not less than 10 per cent of morphine. Dose, 60 mg.

Opium Pulveratum, powdered opium, yields not less than 10 per cent of morphine. Dose, 60 mg.

Tabellæ Codeinæ Phosphatis, codeine phosphate tablets. Dose, 30 mg.

Tabellæ Codeinæ Sulfatis, codeine sulfate tablets. Dose, 30 mg.

Tabellæ Morphinæ Sulfatis, morphine sulfate tablets. Dose, 10 mg.

Tinctura Opii, tincture of opium (laudanum). Each 100 cc. contains not less than 0.95 gram of morphine; absolute alcohol content, about 18 per cent. Dose, 0.6 cc.

Tinctura Opii Camphorata, camphorated tincture of opium (paregoric). Each 100 cc. contains not less than 0.035 gram of morphine along with camphor, benzoic acid and camphor. Dose, 4 cc.

B. P.

Codeina, morphine methyl ether ($C_{18}H_{21}O_3N,H_2O$), colorless, odorless, translucent, crystalline powder with a bitter taste. It is soluble in 120 parts of water and readily soluble in alcohol. Dose, 0.016 to 0.06 gram.

Codeinæ Phosphas, codeine phosphate ($C_{18}H_{21}O_3N,H_3PO_4,H_2O$), colorless, odorless acicular, crystalline powder with a bitter taste. It is soluble in 3.5 parts of water and in 350 parts of alcohol. Dose, 0.016 to 0.06 gram.

Diamorphinæ Hydrochloridum, diamorphine hydrochloride (heroin) ($C_{21}H_{23}O_5N,HCl,H_2O$), colorless, odorless, crystalline powder with a bitter taste. It is soluble in 2 parts of water and in 11 parts of alcohol. Dose, 0.0025 to 0.008 gram.

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EXTRACTUM OPII SICCUM, dry extract of opium, contains 20 per cent of morphine. Dose, 0.015 to 0.06 gram.

LIQUOR MORPHINÆ HYDROCHLORIDI, solution of morphine hydrochloride, contains 1 per cent of morphine hydrochloride, absolute alcohol content about 25 per cent. Dose, 0.3 to 2 mil.

MORPHINÆ HYDROCHLORIDUM, morphine hydrochloride ($C_{17}H_{19}N,HCl,3H_2O$), colorless glistening needles or powder with a bitter taste. It is soluble in 25 parts of water and 50 parts of alcohol. Dose, 0.008 to 0.02 gram.

MORPHINÆ SULPHAS, morphine sulphate ($(C_{17}H_{19}O_3N)_2,H_2SO_4,5H_2O$), odorless, white, acicular crystals or cubical masses or a white, crystalline powder with a bitter taste. It is soluble in 15.5 parts of water and in 565 parts of alcohol. Dose, 0.008 to 0.02 gram.

MORPHINÆ TARTRAS, morphine tartrate ($(C_{17}H_{19}O_3N)_2,C_4H_6O_6,3H_2O$), minute, colorless, odorless crystals with a bitter taste. It is soluble in 11 parts of water and sparingly soluble in alcohol. Dose, 0.008 to 0.02 gram.

OPIUM, opium, contains not less than 9.5 per cent of morphine.

OPIUM PULVERATUM, powdered opium, contains 10 per cent of morphine. Dose, 0.03 to 0.2 gram.

PULVIS CRETÆ AROMATICUS CUM OPIO, aromatic powder of chalk with opium, contains 2.5 per cent of powdered opium equivalent to 0.25 per cent of morphine. Dose, 0.6 to 4 grams.

PULVIS IPECACUANHÆ ET OPII, powder of ipecacuanha and opium (Dover's Powder), contains 10 per cent of powdered opium and 10 per cent of ipecacuanha, the morphine content equalling 1 per cent of morphine. Dose, 0.3 to 0.6 gram.

SUPPOSITORIUM MORPHINÆ. Each suppository contains 0.015 gram of morphine hydrochloride.

SUPPOSITORIUM PLUMBI CUM OPIO, suppositorium plumbi compositum. Each suppository contains lead acetate, 0.2 gram, and powdered opium, 0.06 gram.

TABELLÆ CODEINÆ PHOSPHATIS, tablets of codeine phosphate. Dose, 0.016 to 0.06 gram.

TINCTURA OPII, tincture of opium (laudanum), contains 1 per cent w/v of morphine; absolute alcohol content, about 43 per cent. Dose, 0.3 to 2 mil.

TINCTURA OPII CAMPHORATA, camphorated tincture of opium (paregoric), contains 0.05 per cent w/v of morphine with camphor, benzoic acid, oil of anise; absolute alcohol content, about 58 per cent. Dose, 2 to 4 mil.

TINCTURA OPII CAMPHORATA CONCENTRATA, concentrated camphorated tincture of opium, contains 0.4 per cent of morphine. Dose, 0.25 to 0.5 mil.

TROCHISCUS MORPHINÆ ET IPECACUANHÆ, lozenge of morphine and ipecacuanha. Each lozenge contains about 0.002 gram of morphine hydrochloride and about 0.006 gram of ipecacuanha.

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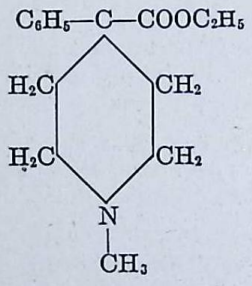
V. OTHER ANALGESICS

Isonipecaine, Meperidine

There has been a never-ending search for drugs that possess marked analgesic properties without producing the side reactions of the opiates. One of these, isonipecaine (pethidine) marketed under the trade name of Demerol (Dolantin), deserves special mention.



Isonipecaine, the ethyl ester of 1-methyl-4-phenyl-piperdine-4-carboxylic acid, was introduced by Eisteb and Schaumann in 1939. It is administered as the hydrochloride salt which is freely soluble in water.

In general, its **pharmacological actions** on the pupil, heart, bronchi, and vagus resemble those of atropine while its effects on bronchi, intestine, and blood-vessels are similar to the spasmolytic effects of papaverine. Resemblance to morphine is seen in its analgesic, sedative, and euphoric properties, and certain of its side effects are similar. In addition, it possesses a slight local anesthetic effect; thus mildly resembling the action of cocaine.

The effect of isonipecaine on the **Central Nervous System** is similar to that produced by morphine. It exerts a generalized depression of central nervous activity. The cough reflex is little affected with ordinary doses (100 mg.) and even with larger doses, respiratory depression is never as great as with morphine. The *vomiting center* is depressed under isonipecaine, but little action is noted on the vasomotor centers with usual therapeutic doses. Euphoria is not uncommon (90 per cent), and this effect may lead to addiction. Relief of pain by isonipecaine is not as effective as with a comparable therapeutic dose of morphine, and the effects are not as persistent. Given parenterally, relief of pain comes on in about fifteen minutes, reaches a peak in forty-five minutes, and subsides in about two hours. The analgesic power of isonipecaine in usual doses is greater than that obtained from 64 mg. of codeine but

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less than from 10 to 16 mg. of morphine. In many instances, isonipecaine is found to be less effective than morphine against sudden acute pain. In addition to its analgesic action, isonipecaine causes sedation and sleep in the presence of pain, but this action is not uniformly present or may even be lacking in about 15 per cent of cases.

The effects of ordinary doses of isonipecaine on the **Respiration** and **Circulation** appear to be negligible. Administered intravenously in dogs, a marked fall in blood-pressure and a sudden decrease in depth and rate of respiration has been reported (Gruber, *et al.*) but these findings are not consistent in man unless advanced cerebral arteriosclerosis is present. Some vasodilatation of the blush area may be noted following therapeutic doses of isonipecaine but are of a transitory nature, the action being a depression of the smooth muscles of the arterioles. The heart rate may be slowed slightly in hypersensitive patients in the upright position, but direct cardiac depression does not occur with ordinary doses. Isonipecaine does not produce the cardiac irregularities in dogs under cyclopropane anesthesia as they are usually seen with morphine (Robbins).

Isonipecaine differs markedly from morphine in its **Smooth Muscle** effects. In man, the stomach, pylorus, small and large intestine, and bronchi are regularly relaxed. The action is partly anticholinergic and partly a direct depression of smooth muscle. The ureter and gall bladder also relax under isonipecaine, but no change in pupil size or accommodation have been noted. While it is said that urinary retention is not common following isonipecaine administration, its effects on the urinary bladder are not clearly defined. Large doses (up to 400 mg.) produce no change in the tonus of the uterus. Whenever isonipecaine relaxes smooth muscle, it does so more readily if the tonus and contractility have been previously increased. It is on this basis that it may be superior to morphine in the relief of pain associated with renal and biliary colic.

Marked **Metabolic** disurbances are not caused by isonipecaine. It is rapidly destroyed by the liver and little of it appears to be excreted in the urine. This probably accounts for its short duration of analgesia as well as its lack of cumulative effects if administered every three or four hours. *In vitro* experiments show that an enzyme present in the liver hydrolyzes the drug. This action is prevented by eserine, but the esterase responsible is not choline or atropine esterase (Bernheim and Bernheim).

Tolerance and **Addiction** to isonipecaine occur, but the incidence is believed to be less than that of morphine. For the most part, tolerance is limited to the analgesic property of isonipecaine and is said to be maximal in about eight weeks (Andrews). In addition, side effects are less pronounced after continued administration of the drug. Addiction studies in man reveal that isonipecaine will not only cause dependence but that it partially satisfies dependence established to morphine. Fortunately, the abstinence syndrome following the withdrawal of isonipecaine is not as severe as with morphine; hence, isonipecaine addiction may more easily respond to treatment.

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Isonipecaine produces **Side Reactions** in about 25 per cent of all patients. Those most commonly reported are dizziness (22 per cent) and sweating (56 per cent). Nausea and vomiting occur with less frequency (4 to 8 per cent) as does headache. In a few individuals (5 per cent) a "nitritoid" syncope occurs, but this condition is only temporary and is rarely seen in the non-ambulatory patient. In this connection, the other effects noted above occur with greater frequency in the ambulatory as compared with the hospitalized bed-patient. It does have the advantage over morphine of not causing pruritus.

Large, repeated doses of isonipecaine cause **Toxicity** attributable to cerebral irritability, and convulsions may occur. In this regard, the picture is similar to that seen in atropine poisoning since dilatation of pupils, disorientation, tachycardia, and muscle twitchings are not uncommon. Serious respiratory depression may result from large doses repeated at less than three to four hours apart. However, these symptoms are not noted with ordinary therapeutic use and isonipecaine appears to have a wide margin of safety although the fatal dose in man is not known. Recent evidence suggests, however, that isonipecaine may, like morphine, be biphasic relevant to its central actions. Furthermore, experimental data would caution the use of isonipecaine with barbiturates in premedication since the latter potentiate the depressive properties of the former upon respiration even though they seem to antagonize the lethal convulsive effects.

The indications for the **Use** of isonipecaine are similar to those of morphine. It is best given intramuscularly since subcutaneous injections may be irritating and its intravenous use is more apt to cause unpleasant side reactions. It is absorbed from the gastro-intestinal tract, but its efficiency is reduced by oral administration. The usual adult dose is 100 mg. repeated at three to four hour intervals, while for children the dose range is 10 to 75 mg. Because of its antispasmodic effect, it is indicated in colicky pains. Isonipecaine may be superior to morphine as a pre-anesthetic agent since respiration is less affected and urinary retention is less common. It potentiates the action of the barbiturates as does morphine and provides a more pleasant induction while, at the same time, the amount of general anesthetic required is reduced. Experimental data suggest that isonipecaine should be used prior to cyclopropane anesthesia (p. 303). It is of definite value in acute and chronic bronchial asthma, but the possibility of addiction when used for this purpose must be kept in mind. It seems indicated in pneumoencephalography, in whooping cough, and in habitual vomiting in children because of its sedative action on the vomiting center. Time alone will substantiate the claim that isonipecaine is a substitute for morphine; at the present time such proof is lacking.

COMPARISON OF ANALGESICS

Drug	Usual dose mg.	Analgesic potency	Respiratory depression	Constipative effect	Euphoria	Addiction tendency
Morphine . .	16	++++	++++	++++	+++	++++
Codeine . .	30	++	+	++	+	++
Dilaudid . .	2	++++	+++	+++	+++	++++
Isonipecaine .	100	+++	++	–	+++	+++

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Cobra Venom has been recommended as an analgesic particularly by Macht. The average hypodermic dose in man (10 mouse units, 1 cc.) usually causes few untoward effects but nausea and vomiting, diarrhea, and pain at site of injection may occur. In experimental animals, large doses cause a fall in blood-pressure, while minute amounts (6 to 9 micrograms per kg.) effect a prolonged rise. Large doses cause respiratory failure due to medullary paralysis. Cobra venom lacks the excitatory action of morphine when administered to cats.

In man, with ordinary doses, the analgesic effect is less rapid than with the opiates but is more prolonged. According to Macht, cobra venom acts centrally on the pain centers of the brain without depressing the special senses or altering the nerve impulses of ascending or descending fibers.

Cobra venom has been tried as a substitute for morphine in the relief of pain with varying results.

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VI. CANNABIS

The hemp plant, cannabis sativa, grows readily in warm climates such as India, Egypt, Mexico, or the southwestern section of the United States. It has been eaten to produce inebriation by peoples in the Orient since time immemorial, under the names of *Hashish, Bhang, Ganja, Charas,* or *Churrus.* Some of the preparations are smoked either alone or mixed with tobacco; others form an intoxicating drink, while in others it is mixed with sugar or honey and taken as a confection. During the last decade and especially since 1935, the practice of smoking cigarettes, containing Indian hemp under the name of "Marihuana," has become increasingly prevalent in some parts of the United States and to a less extent in Canada and England. In the southwestern area of the United States and in Mexico, the marihuana habit has become more of a problem than any other drug habit. The vice is not uncommon in adolescents and even in children and there appears to be some relationship between the incidence of the habit and crime. The authorities concerned have taken steps to stamp out the practice. The problem has recently been reviewed by Walton who has given a historical account of addiction to Indian hemp with an exhaustive bibliography.

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The active principle of Indian hemp has been found to be a red oil or resin boiling at a high temperature (Cannabinol); this was found by Marshall to induce the typical effects of cannabis in man and animals. Frankel states that cannabinol is a phenolaldehyde of the formula: $OHC_{20}H_{28}COH$.

According to Loewe, the active principle of cannabis will produce ataxia in the dog and corneal areflexia in the rabbit, but there are other substances in hemp which will independently cause one or both of these effects as well.

Symptoms.—The effects of cannabis are similar no matter whether it is eaten as the crude drug or smoked in cigarettes. They consist chiefly in a mixture of depression and stimulation similar to that seen under small doses of morphine. Soon after its administration, the patient passes into a dreamy, semi-conscious state, in which the judgment seems to be lost, while the imagination is untrammeled by its usual restraints. The dreams assume the vividness of visions, are of boundless extravagance, and of course, vary with the character and pursuits of the individual. Ideas flash through the mind without apparent continuity, and all measurement of time and space is lost. True hallucinations may appear, but are often absent. During this period the consciousness is not entirely lost, for the patient often feels that his dreams are unreal, his satisfaction unfounded, and his movements ridiculous, but he cannot restrain them; he can give a coherent account of his condition when aroused and answer questions intelligently. The sensation of pain is lessened or entirely absent, and the sense of touch is less acute than normally. Later the dreams alternate with periods of complete unconsciousness, from which the patient can be aroused easily, and the symptoms eventually pass into tranquil sleep from which he awakens refreshed and, as a rule, without any feeling of depression or nausea. In the majority of cases, the preliminary stage of exaltation is very short or entirely absent. According to Dixon, the drug may be more exhilarating when inhaled than when swallowed, and this may account for some of the variations in its action. In some cases, acute mania and convulsive attacks have been developed, and among the natives of India, catalepsy occasionally occurs.

Death from acute poisoning is extremely rare, and recovery has occurred after enormous doses. The continued abuse of hashish in the East sometimes leads to mania and dementia, and some tolerance is rapidly acquired.

Therapeutic Uses.—Cannabis has been used as a hypnotic in cases of sleeplessness from nervous exhaustion and, less often, from pain, but preparations of it are no longer official, and it possesses no therapeutic indications.

The fluid preparations are used most extensively with salicylic acid in "corn" remedies, but the acid is the active ingredient in such combinations.

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Mescaline (trimethoxy-phenyl methylamine).—A number of alkaloids, some resembling morphine, others like strychnine in their effects on animals, have been isolated from different members of a small cactus, Lophophora williamsii (formerly Anhalonium lewinii). In Mexico and along the southern boundary of the United States where these plants are indigenous, some of them are used as narcotics in the religious rites of the Indians and are known as Peyote or Mescal Buttons. The symptoms arise for the most part from the cerebrum and differ from those of opium and cannabis in the frequency with which color visions are induced, these consisting of constantly shifting flashes of brilliant tints. Mescaline does not induce merriment like cannabis nor sleep like morphine, but depression of some functions is indicated by the imperfect coördination of the movements, the retarded perception, and the errors in the estimation of time. The exaltation seems to be caused for the most part by one of the alkaloids,

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mescaline. Very large doses have induced unpleasant symptoms through depression of the respiration. Peyote is said to produce a peculiar pelvic band of analgesia and is used by some Indian tribes in obstetrics on this basis. Tainter, *et al.* found that mescaline raised the convulsive threshold in rabbits.

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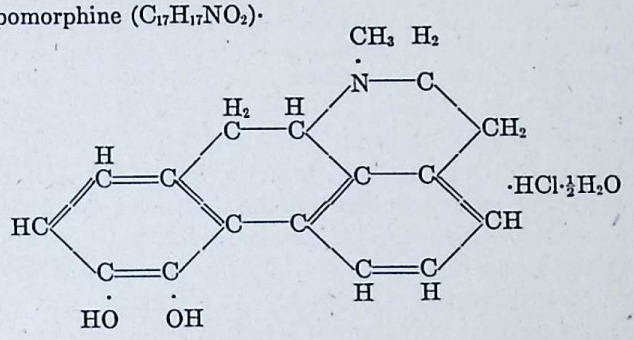
VII. APOMORPHINE

When morphine is acted on by acids and by some other dehydrating agents, it loses a molecule of water, and a new alkaloid is formed,

Apomorphine ($C_{17}H_{17}NO_2$)·



Through this change, the action of the original alkaloid is considerably modified; apomorphine preserves the stimulant but loses to a great degree the depressant action of morphine on the central nervous system. This stimulant action extends over the whole central nervous system in animals, but is most developed in the "vomiting center" of the medulla oblongata.

Symptoms.—In man, apomorphine in doses of 5 to 10 mg. induces within ten to fifteen minutes nausea and vomiting. Very often the nausea passes off immediately after the evacuation of the stomach, but when larger quantities have been administered, repeated vomiting and retching may occur. Occasionally depression and sleep follow the emesis after even small doses.

The attendant symptoms are profuse salivation, increased secretion of the mucous glands of the nose, throat, and bronchial passages, tears, and a cold perspiration. A feeling of depression and muscular weakness and acceleration of the pulse are also well-known symptoms accompanying nausea and vomiting and are present after apomorphine. These are all to be regarded as sequelæ of the emetic action, however, and not as due to the direct action of the drug on the glands and other organs. In a few instances, the depression and weakness have passed into alarming collapse, but no actual fatality is recorded from the use of apomorphine.

Very small doses of apomorphine may induce the secondary symptoms without actual vomiting. Thus the saliva, perspiration, tears, and

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other secretions may be augmented by quantities which are too small to act as emetics.

Apomorphine induces vomiting through changes in the medulla oblongata and not by irritation of the stomach. This is shown by the fact that it acts much more quickly and in smaller doses when it is injected hypodermically or intramuscularly than when it is swallowed and also by the fact that if the medulla is brushed with apomorphine solution, vomiting follows immediately. The movements of vomiting may also be induced in animals after the removal of the stomach and intestines.

In addition, large doses of apomorphine can cause depression of the central nervous system to the extent that no emesis occurs.

Apocodeine is formed from codeine in the same way as apomorphine from morphine, but it differs entirely from apomorphine in its action and resembles nicotine in paralyzing the sympathetic ganglia. It causes purgation when injected hypodermically, apparently from removing the normal inhibition of the bowel movements (Dixon). If codeine is heated with hydrochloric acid, apomorphine is formed and not apocodeine.

Therapeutic Uses.—Apomorphine is used chiefly as an emetic and presents several advantages over other drugs employed for this purpose, inasmuch as it acts more promptly and can be administered by the hypodermic needle, while most of other emetics (ipecac and emetine excepted) cause vomiting by irritating the stomach and have to be given by the mouth, which is a serious drawback in cases of poisoning. The more important of these older drugs are ipecac, ammonium carbonate, the sulfates of copper, zinc, and alum.

Vomiting is not now such an important method of treatment as it was formerly, and the emetics are less frequently employed to evacuate the stomach than other measures, such as repeated washing of the stomach by means of the stomach tube. In narcotic poisoning, apomorphine not infrequently fails to act, owing to the depression of the vomiting center, and in corrosive poisoning, a certain amount of danger attends its use as the pressure on the walls of the stomach exerted by the contraction of the diaphragm and abdominal muscles may lead to the rupture of the weakened walls of the organ. In addition, the collapse phenomenon seen after apomorphine may be additive enough to the condition already present to cause serious coma; consequently, apomorphine must be used judiciously at all times.

As an expectorant, apomorphine may be prescribed in 1 mg. doses in a pleasant tasting elixir or syrup preparation, or it may be given hypodermically in a similar dosage.

Of interest is the use of subemetic doses of apomorphine as a sedative in emergence delirium, acute alcoholic psychosis, and as a pre-anesthetic prior to operations in persons suffering from severe excitement and agitation accompanying morphine addiction. As a rule, 1 to 2 mg. are given intravenously in sterile normal saline. Effects come on in about ten minutes and last two hours. Where asphyxia or oxygen want is present, apomorphine is contraindicated (Rovenstine and Hershey).

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PREPARATIONS

APOMORPHINÆ HYDROCHLORIDUM, apomorphine hydrochloride ($C_{17}H_{17}O_2N.HCl.\frac{1}{2}H_2O$) (U. S. P., B. P.), occurs as white or grayish white crystals which turn a greenish color on exposure to light and air; soluble in 50 parts of water and alcohol. Dose, 5 mg. (U. S. P.), 0.001 to 0.002 gram (B. P.).

Caution.—Apomorphine hydrochloride must be rejected if it at once imparts an emerald green color to 100 parts of distilled water when shaken with it in a test-tube.

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Bulbocapnine

Bulbocapnine is the most important of several alkaloids found in *Corydalis cava.* It is closely allied in constitution to apomorphine, being 3:4 methylenedioxy-6-methyl-apomorphine ($C_{19}H_{19}O_4N$).

It was first investigated pharmacologically by Peters in 1904, who found that it produced a peculiar *cataleptic* condition in mammals. The limbs became stiff, and accompanying a sustained tonus of the muscles, voluntary and reflex movements were abolished though there was no increased resistance to passive movements.

The cataleptic symptoms do not occur in cold-blooded animals; instead, bulbocapnine produces a morphine-like action. The action in mammals varies according to the species and the dosage. Catalepsy is more pronounced in more highly developed mammals, *e. g.*, monkeys, dogs, and cats. The stiffness of the limbs is central in origin and has been ascribed to tonic labyrinthine reflexes. In spinal cats, bulbocapnine causes an increased tone in the flexor and extensor muscles of the hind limbs (Ward and Kolb). Larger doses cause narcosis with eventually complete loss of motility, and the alkaloid increases the action of hypnotics, *e. g.*, phenobarbital and paraldehyde.

Some of the symptoms suggest also a stimulant action of the *parasympathetic* nervous system, *e. g.*, salivation, lacrimation, micturition, and defecation; but in intact animals, bulbocapnine acts like a *sympathetic* agent, causing a diminished amplitude of intestinal contractions.

Bulbocapnine causes a fall of blood-pressure with vasodilatation. Some of the vascular reflexes in the rabbit's ear are abolished; the pressor action of epinephrine is diminished but not reversed. Of interest is the work of Feldman, *et al.*, who reported that bulbocapnine produced hyperglycemia in normal rats and in such animals whose vagi were cut. This work indicates that both the vago-insulin and sympathetico-adrenal systems were stimulated; in this respect, cocaine acts similarly.

Hence, bulbocapnine possesses sympathetic as well as parasympathetic central effects, but it is not possible to predict which effect will predominate.

Bulbocapnine has been used from time to time to control the tremors in paralysis agitans and postencephalitic conditions. It has also been recommended for the relief of vertigo in Ménière's disease and for the suppression of choreiform movements. Clinical results following bulbocapnine have not been very satisfactory, and it remains a drug of greater academic than of practical interest.

A usual dose is 0.1 gram orally once or twice daily and as much as 0.5 gram has been administered without toxic effect.

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VIII. BROMIDES

In a few respects the bromides have no further action than the corresponding chlorides, and any effects observed from inorganic bromine salts are due to the cation, the bromide ion being indifferent. However, the bromide ion also has distinctive effects for it induces changes in the central nervous system which are not elicited by the chlorides. It is these latter effects which are of pharmacologic and therapeutic interest.

The **Local Action** of the bromides on the alimentary tract is the same as that of sodium chloride and other salts; *i. e.*, withdrawing fluid from mucous membranes. They have a bitter salt taste and induce salivation and thirst, and in large quantities, irritation of the stomach with nausea and vomiting. Occasionally diarrhea has been observed from concentrated solutions reaching the intestine.

General Symptoms.—The usual dose of bromides, 1 to 2 grams, produces a feeling of calmness, removes the sense of worry, and as rule, sleep follows. Prior to sleep, thoughts may be slow and somewhat confused and memory is indistinct. Ideas are put into words with difficulty, and the speech is accordingly slow and hesitating. External objects and movements are perceived but arouse no interest in the patient, and very often this state of apathy then passes into drowsiness and sleep. The bromides, however, have not the sleep-compelling power of chloral, and the sleep is never as deep or refreshing, the patient sometimes feeling dull and unfit for exertion after it and some mental confusion often persisting for several hours after waking. After larger doses, 3 to 4 grams, the reflexes are much depressed so that touching the back of the throat does not induce nausea although the sensation of touch may persist. The mucous membranes of the genito-urinary tract are also less sensitive, or rather their irritation is less liable to set up reflex movements. After very large doses of the bromides, the conjunctiva may sometimes be touched without causing winking, and lessened sensation in the skin has been noted in some cases. The pulse and respiration are slower than usual after large doses but scarcely more so than in sleep. An increase in the urine is often observed. In addition, apathy and lassitude become marked, and mental dullness is marked so that orientation and fixation of ideas is not possible of attainment.

The most important actions of the bromides on the **Central Nervous System** are general depression, reduction in motor irritability, and suppression of reflexes. Albertoni found that the irritability of the motor areas of the dog's brain was very distinctly reduced by the administration of bromides and in particular, that a stimulus which normally would have spread over a wide area and given rise to an epileptiform

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convulsion caused only localized contractions after bromides, while convulsive poisons entirely failed to act. Some psychical processes, such as those involved in the addition of numbers, are uninfluenced by bromides while figures are learned by rote only with great difficulty. Therefore, one may consider that the action of bromides is limited to certain definite functions. The *reflexes* are also reduced very considerably by bromides, and according to many observers, the passage of impulses from the sensory to the motor cells of the cord is interrupted while the connection between the cerebral centers and the motor cells of the cord is maintained intact. In man, the most striking instance is the absence of reflex nausea when the back of the throat is touched. While reflex movements cannot be elicited, the sensation often remains unimpaired, but after large doses, a more or less complete anesthesia is said to be produced. This anesthesia extends to the skin when very large quantities are administered, and the cutaneous sensation is said to be blunted when comparatively small doses are taken. This action is purely central because the peripheral sense organs remain unaffected. However, effects other than those directly attributable to the central nervous system have no practical importance and must be considered as indirect, undesirable effects.

The *respiration* is slower under bromides, owing to the lessened movement but is scarcely more reduced than in normal sleep, and with usual doses, the *blood-pressure* and *pulse* are scarcely affected. The *sexual instincts* are depressed or entirely suspended, either from the action on the brain or from the lessened reflex activity.

The bromide ion is almost as indifferent to most of the tissues as the chloride. For example, *muscle* and *nerve* live almost as long in solutions of sodium bromide as in those of the chloride of equivalent concentration, and the heart may be perfused with saline containing bromide instead of chloride for many hours and be only slightly affected. All cells except those in the brain seem indifferent to the substitution of bromide by chloride. The nerve cells, however, respond to bromides so that by means of the electroencephalograph, it is noted that they inhibit the development of abnormal wave patterns characteristic of petit mal.

Flinn, Trowbridge, *et al.*, and Jellinek and Bolles have carefully studied patients after administering 1 to 2 grams daily for a period of several months. No change was noted in the nervous reactions, light adaptation, electrocardiogram, pulse rate, blood-pressure, blood counts, or CO_2-combining power. Large doses, 3 to 5 grams, produced only sedative effects upon perception, spatial orientation, and similar psychological functions. However, many clinicians are of the opinion that a daily dose of 2 grams over a period of four to six months will eventually lead to definite mental deterioration and produce untoward neurological changes in the average patient.

Distribution and Excretion.—The bromides are rapidly absorbed by the mucous membranes, and a bromide reaction can be obtained from the urine a few minutes after they have reached the stomach. Their distribution in the body resembles exactly that of the chlorides; thus, they are found in largest amounts in the blood plasma and have little tendency

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to accumulate in the organs. They occur in all the secretions and fluids of the body; they may be found in the form of hydrobromic acid in the stomach, and traces are found in the sweat and milk and in the hair, where chloride occurs naturally. The brain and spinal cord do not contain larger quantities than the other organs and never approach the amount contained in the blood plasma; the skin appears to contain a larger amount than most other organs.

The whole behavior of the bromides in the body indicates that most of the tissues are unable to differentiate them from the normal chloride ions and react to a dose of bromide in the same way as to one of common salt. Thus the administration of bromide is followed by the excretion of an equivalent amount of salt, and the kidney does not discriminate between the two forms circulating in the blood, *but* eliminates a mixture of chloride and bromide exactly in the same proportion as these occur in the blood. If it were possible to follow the course of the individual ions in the body after a dose of common salt, it would probably be found that although an equivalent amount of salt is soon eliminated in the urine, the actual chloride ions taken would only be represented in this excretion to a limited extent, the rest being furnished by that previously present in the blood and tissues; the remaining new chloride would gradually be eliminated in diminishing proportions. This is what occurs with bromides; at first the amount excreted bears a high proportion to that of the chloride, but this falls off rapidly, and some bromide appears in the urine for long afterward. Thus, after a single dose of 2 grams, the urine was found to contain bromide for two months, only about 10 per cent being eliminated in the first twenty-four hours. When the treatment is continued, the bromide therefore tends to accumulate in the body, and the proportion excreted rises with the increase of the drug in the blood until an equilibrium is reached, exactly as much bromide appearing in the urine as is absorbed from the bowel. The excretion then continues long after the treatment is discontinued. It is obvious, therefore, that the bromides possess a cumulative action and hence may easily cause toxic effects if administered over a long period of time. In the presence of kidney dysfunction, cumulative effects are even more apt to occur.

When the body is thus saturated with bromide, the blood plasma and all the fluids may contain as much bromide as chloride; for example, the gastric juice may contain even more hydrobromic acid than hydrochloric acid. The bromides are not simply added to the normal salts of the blood but supplant the chlorides, which are excreted in quantity so that the normal salt concentration of the blood is maintained though the chloride is much diminished. During bromide treatment, therefore, and especially in *bromism*, not only is there an excess of bromide in the body but also a deficiency of chlorides, and it has been much discussed whether the symptoms of bromism and the sedative effects of bromide arise from the action of the bromide directly or are the results of the deficiency of chloride. However, two acknowledged facts appear to prove that the bromides do possess a definite action on nerve cells apart from any action due to a deficiency of chlorides. First, the

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administration of chloride promotes the excretion of bromide and thus lessens the concentration of bromide in the fluids of the body, and secondly, it has been found that animals may be narcotized with bromide quite rapidly long before it is possible that a serious fall in the chlorides of the blood has occurred. In practice, however, the bromide action is accompanied by chloride poverty, and on the other hand, any excess of chloride reduces the concentration of bromide and thus interferes with its action. The same is true of other measures which tend to withdraw bromide, such as the use of diuretics.

Wallace and Brodie found that bromides injected intravenously in dogs at once entered the spinal fluid but that the serum always contains a lower concentration of bromine ions than the spinal fluid while the reverse is true of the chlorine ion. They suggested that there is a selectivity factor in the passage of these ions into, and perhaps from, the spinal fluid.

Poisoning.—Acute fatal poisoning with bromides has seldom or never occurred in man since large amounts usually cause vomiting due to an irritant action on the stomach. After enormous doses, prolonged sleep, or stupor has been seen, and confusion and apathy may last for several days.

Chronic poisoning, often called *bromism,* caused by bromides, has materially increased during the past ten years due to the indiscriminate use by the laity of certain proprietary medicines. In addition, long continued administration of bromides to patients with epilepsy often results in chronic bromide intoxication. Physicians sometimes carelessly prescribe bromides, and hence they must always be cognizant of the possibility that bromides often cause cumulative poisoning and must learn to recognize bromism and the attendant manifestations.

The *incidence* of psychosis due to chronic bromide intoxication is reflected in the admission of patients to psychiatric wards. Reports from various clinics suggest that from 2 to 10 per cent of all psychotic patients suffer from bromide poisoning, and a figure of 20 per cent may be more nearly correct if careful histories are taken and blood bromides are determined. As a rule, psychoses due to bromides are more common in men than in women and are more often seen in the third and fourth decades of life (Moore and Gray).

According to Curran, 66 per cent of all patients suffer from *delirium* characterized by speech disturbances, visual hallucinations, memory defects, vestibular disturbances, marked mental confusion, and more rarely micrographia and micropsia. Alterations in speech are of a paraphasic nature, and the visual hallucinations in contrast to those of the alcoholic are distant rather than near at hand. In addition, some patients exhibit a typical Korsakoff syndrome while others show a toxic state with neurological symptoms similar to general paresis. Various *neurological signs* are usually present in persons suffering from bromism, but they are inconstant in their appearance. The depression of deep as well as superficial reflexes is seen most often, especially of the mucous membranes and skin. Tremors of the fingers and lips are also common, and apraxia due to disturbances in central innervation is often observed. The *pupils* are usually dilated and react sluggishly to light. Tachy-

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cardia is not uncommon, and a rise of temperature (1 to $1\frac{1}{2}$° C.) is often seen in the dehydrated individual.

In many patients, *digestive disturbances* are a common finding. Among the common symptoms may be mentioned: gastritis, chronic constipation, and anorexia, all of which may lead to emaciation and weakness due to an improper food intake. Like the iodides, bromides may stimulate various *secretions*. Catarrh of the respiratory tract, excessive tear formation, and a condition similar to the common cold are often noted. The mechanism of action is probably due to the presence of the bromides in the various secretions and not to any specific action on the gland cells themselves. A typical bromide rash (Fig. 26) is *not* common

FIG. 26.—Common form of bromide eruption. (Ormsby and Montgomery's Diseases of the Skin, Lea & Febiger.)

in chronic bromide poisoning, and if more attention was given to a proper neurological rather than a dermatological examination, many patients would be earlier benefited. If a skin eruption does occur, it is usually acneiform in character and is more often seen on those parts of the body supplied by the fifth cranial nerve and the cervical plexus. Of recent interest is the report of *hyperglycemia* and *glycosuria* accompanying a severe case of bromide intoxication (Pilkington).

There is a marked variation in the *susceptibility* of individuals to bromides. In general, it may be said that patients who suffer from arteriosclerosis or mental depression and those who are undernourished or use salt sparingly on their food are more apt to show evidences of bromide intoxication. In addition, persons in equal good health and on a normal diet who are taking daily doses of bromides vary with respect to the length of time that is required for the appearance of chronic bromide intoxication. Because of these modifying factors, bromide poisoning must finally be diagnosed on the basis of the bromide blood level. Simple chemical tests have been devised (Wuth and Hanes and Yates) and a routine blood analysis should be made on all persons who are suspected of suffering from bromide intoxication and in those who are receiving treatment in the form of bromide therapy. While there is no definite correlation between blood bromide levels and the toxic symptoms of bromide poisoning, one may usually expect the occurrence of untoward manifestations when 25 to 30 per cent of the

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chlorides in the blood are replaced by bromides; *i. e.*, a blood bromide of more than 150 mg. per cent. Epileptics have a higher tolerance for bromides, and levels higher than 200 mg. per cent have been recorded in the absence of toxic symptoms. Rubin and Cohen found that blood bromide levels of 59.6 mg. per cent lowered the alpha rhythm of the occipital lobe but that a higher frequency approaching normal was maintained at a level of 36.7 mg. per cent.

The *treatment* of chronic bromide poisoning consists chiefly in abrupt withdrawal of the drug plus the administration of sodium chloride so that the bromide may be more quickly eliminated. The salt intake of the diet should be increased and, in addition, sodium chloride may be administered orally in daily doses of 20 grams or more depending upon the tolerance of the individual to such therapy. As the patient improves, the amount may gradually be reduced. When necessary, sterile physiological saline may be administered intravenously. Even when an adequate intake of sodium chloride is maintained, recovery is not usually complete before about twenty-one days of treatment. In addition, a fluid intake of about 4,000 cc. per day should be instituted. In the early phase of treatment, hydrotherapy and wet packs are often helpful aids in many patients. Finally, many cases of bromide intoxication are due to self-medication of the drug, and hence after recovery from the intoxication, attention must be directed toward the treatment of the underlying mental disorder for which the bromide had been used.

Therapeutic Uses.—In order to be most effective, the bromides must be given for several days in order that an effective concentration of bromide ion be reached and maintained. Hence single doses of bromides (1 to 2 grams) are less useful as *sedatives* than chloral hydrate, the barbiturates, or paraldehyde. Bromides are still useful where it is necessary to administer them clinically to produce sedation and sleep; *i. e.*, seasickness, vomiting of pregnancy, chorea, anxiety states, hyperthyroidism, restlessness due to cardiac disorders, and sexual hyperesthesia. In any case, it should be emphasized that the bromides are not effective sedatives in the presence of pain.

Bromides were the first effective drugs to be used in the treatment of *epilepsy* and even though phenobarbital, dilantin, and tridione have been introduced for this purpose, the bromide salts are still used extensively.

The treatment of epilepsy requires skill and judgment on the part of the physician. The patient, not just the patient's symptoms, must be treated, and measures which prevent the whole seizure and not just a part of an epileptic attack must be instituted. In each new patient, the important problem is to ascertain if the drug used really benefits the patient. If it does not help the patient, then the physician must have the good sense to stop it and try another. It is not possible to predict the time when seizures may occur, and hence drugs must be given daily in order that an effective concentration of the drug in the body is always maintained.

It is quite easy to maintain a constant bromide blood level since this drug is slowly excreted. As a rule, the effective level of bromide in the

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blood for most epileptics is 100 mg. per cent, but some patients have their symptoms ameliorated when a level of only 75 mg. per cent is maintained while others require as much as a level of 200 mg. per cent. In any event, the physician should administer the minimal amount of bromide which will optimally control the epileptic attacks, and repeated blood levels serve as a guide to insure adequate dosage and to prevent bromide intoxication. In addition, the patient should be placed on a rather stable salt intake to prevent undue fluctuations in the blood bromide level.

The bromides do not cure epilepsy, but they do reduce the number and intensity of attacks, and complete remissions of more than a year are often seen in over 50 per cent of patients who have been properly treated for the grand mal variety of epilepsy. The bromides are not as effective against the petit mal as the grand mal type of attack. In addition, psychic equivalent attacks or seizures due to a focal infection or to head injuries are not very responsive to the administration of bromides. One of the disadvantages of the bromides in epilepsy is that some sedation occurs before optimal effects may be obtained—hence, it is all the more important that the physician administer the minimal effective dose if the patient expects to carry on his daily work.

The usual daily dose of a bromide which will insure an adequate blood level varies between 1.5 to 3.5 grams. Sodium bromide in a pleasant tasting syrup is preferred, and experience has shown that the total daily dose is best administered in three equal parts after meals. Triple bromides offer no advantage over the single salt of bromide and have the disadvantage of being more expensive.

The bromides are *contraindicated* in arteriosclerosis, kidney disease, cachexia, dehydration, and in old people since poisoning is more apt to occur in these conditions due to a lessened excretory power of the kidney. In addition, bromides should be used cautiously in any mental disturbance until a definite diagnosis has been made. Such a procedure often prevents the development of bromism because once a patient commences using a bromide, he often indiscriminately practices harmful self-medication. Finally, bromides, like iodides, are contraindicated in tuberculosis since they may "light up" a dormant lesion.

The bromides are not so effective in other affections of the central nervous system although some success has attended their use in chorea, in the convulsions of children, and in some forms of hysteria. They have also been tried in tetanus and in strychnine poisoning but are inferior to other remedies, such as chloral and the derivatives of barbituric acid. Neuralgia is sometimes improved by bromide treatment, especially when it arises from worry, anxiety, or overwork. In sleeplessness from anxiety, they are often valuable, however, and it is found that the dose of chloral may be considerably lessened if it is prescribed along with bromides. Of recent interest is the use of strontium bromide intravenously (1 gram in 10 cc. of saline) for the relief of bronchial asthma (King).

Brometone.—Tribromtertiarybutylalcohol—$CBr_3C(OH)(CH_3)\cdot CH_3$—1,1,1-tribrom-2-methyl-propan-2-ol (N. N. R.). The action of this

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substance is similar to that of the bromides, but it is less apt to cause bromism. Its action is prompt and lasts for several hours. Ordinary doses of 0.3 gram in capsules cause no unpleasant side reactions. Larger doses cause anorexia, vertigo, and mental confusion. It has been used in insomnia, cough, epilepsy, and labyrinthine disturbances.

Bromural.—$(CH_3.CH(CH_3)CHBr.CO)HN.CO.NH_2$—2 monobromisovalerylurea (N. N. R.). Bromural is a mild sedative producing sleep lasting three to five hours. It is useful in functional nervous disease but is of no value if pain or discomfort is responsible for the insomnia. The usual dose is 0.3 gram three times daily orally as tablets, or 0.6 gram as a hypnotic at bedtime.

Carbromalum, N. F. and B. P., brom-diethylacetyl urea, $(C_2H_5)_2CBr.CO.NH.CONH_2$, is a moderately powerful hypnotic, relatively free from after-effects and used mostly in insomnia due to worry, overwork, or excitement. It is known by the trade names of Adalin and Uradal.

PREPARATIONS

CARBROMALUM, carbromal (uradal) $(CBr(C_2H_5)_2.CONHCO.NH_2)$, (B. P.), a white crystalline powder with little odor or taste. It is soluble in 3,000 parts of water and 18 parts of alcohol. Dose, 0.3 to 1 gram.

POTASSII BROMIDUM, potassium bromide (KBr), (U. S. P., B. P.), occurs as colorless, transparent crystals or as a white granular powder and has a saline taste. It is soluble in about 2 parts of water and in about 200 parts of alcohol. Dose, 1 gram (U. S. P.), 0.3 to 2 grams (B. P.).

SODII BROMIDUM, sodium bromide (NaBr), (U. S. P., B. P.), occurs as white, odorless, cubical crystals or as a white granular powder with a saline taste. It is soluble in about 1.2 parts of water and 16 parts of alcohol. Dose, 1 gram (U. S. P.), 0.3 to 2 grams (B. P.).

TABELLÆ CARBROMALI, tablets of carbromal (B. P.). Dose, 0.3 to 1 gram

TABELLÆ POTASSII BROMIDI, tablets of potassium bromide (B. P.). Dose 0.3 to 2 grams.

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IX. ANTICONVULSANTS

Diphenylhydantoin Sodium

Although the bromides and phenobarbital have been effective in the treatment of certain forms of epilepsy, they are incapable of anticon-

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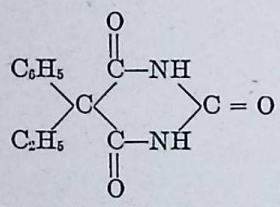
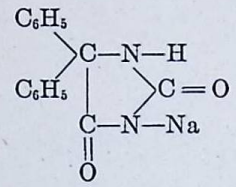
vulsant action without causing an undesirable sedative and hypnotic effect. Diphenylhydantoin sodium was introduced by Merritt and Putnam in 1938 for the treatment of convulsive disorders after experimental results and clinical experience had shown that it was a superior anticonvulsant when compared with the bromides, was equal or more effective than phenobarbital in this respect, and did not possess the hypnotic action of either. This compound is sometimes referred to as phenytoin sodium, and it is marketed under the trade name of Dilantin Sodium.

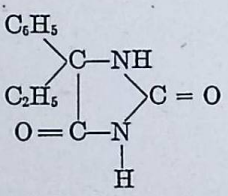
Chemically, diphenylhydantoin sodium is related to phenobarbital and to nirvanol, a non-official preparation sometimes used to treat chorea in children (p. 377).



Phenylethylbarbituric acid



Diphenylhydantoin sodium



Phenylethylhydantoin (nirvanol)

It may be said that diphenylhydantoin sodium possesses the useful anticonvulsant activity of phenobarbital and many of the untoward effects of nirvanol.

The **Actions** of diphenylhydantoin sodium other than its therapeutic effect have largely been described in animals. When administered intravenously, it was found to be quite toxic to dogs, rabbits, and rats. There was usually a marked fall in blood-pressure, respiration was decreased in amplitude and frequency, and the vagus nerve was temporarily depressed. When death occurred, the cause was due to respiratory paralysis or convulsive asphyxia. Among other symptoms noted were nystagmus, mydriasis, salivation, hyperpyrexia, muscle tremors, and vomiting (Haury and Drake and Gruber, *et al.*). When animals are given very large doses orally over a long period of time, however, few if any symptoms appear, and no changes in behavior are noted. Experimentally, diphenylhydantoin sodium prevents anoxic convulsions and improves the altitude tolerance of mice, either administered alone or in combination with neostigmine (Emerson and Hoff and Yahn).

No exact statement can be made regarding the *mechanism* whereby diphenylhydantoin sodium prevents epileptic seizures in man or experimentally induced convulsions in animals. It appears that the motor cortex is specifically affected since depression of other central functions

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is rarely seen. However, many epileptics show a distinct improvement in general behavior, are more alert, can concentrate better, and show an increased ability for work after proper therapy with diphenylhydantoin sodium. These facts plus results suggesting that psychic equivalent attacks are benefited suggest that certain other areas of the **Central Nervous System** are affected by diphenylhydantoin sodium (Robinson). Finally, diphenylhydantoin sodium diminishes the convulsions induced by metrazol in man, but single doses do not inhibit metrazol convulsions in experimental animals (Goodman and Lih).

The question as to whether diphenylhydantoin sodium merely *prevents* attacks of epilepsy or corrects the dysrhythmia responsible for the disease is not yet settled. Electroencephalography indicates that improvement in rhythm does not necessarily parallel clinical improvement. As a matter of fact, patients who are symptom-free may exhibit a dysrhythmia as shown by electrical records as severe as before treatment. However, clinical improvement as well as a return to normal rhythm is often seen in persons with psychomotor seizures.

The **Fate** of diphenylhydantoin sodium in the body is unknown although most of it appears to be destroyed or altered since only a very small percentage (less than 0.2 per cent) is excreted in the urine.

The **Therapeutic Use** of diphenylhydantoin sodium is chiefly confined to the treatment of epilepsy. It is definitely more effective in the grand mal than in the petit mal type of epilepsy and has given better results than phenobarbital or the bromides in the treatment of psychic equivalent attacks. In addition, it is often of value after other drugs, and other methods including a ketogenic diet régime have failed to alleviate the symptoms of epilepsy. As with the bromides, diphenylhydantoin sodium does not immediately affect a change in the epileptic patient. Several days must elapse until a constant concentration in the body is reached before improvement will be noted.

Early reports indicate that diphenylhydantoin sodium would give about 60 per cent complete relief in grand mal and about half as good results in the petit mal type of epilepsy (Merritt and Putnam). More recent studies by Robinson and Weinberg and Goldstein report marked reduction or complete cessation of seizures in 39 to 40 per cent of their grand mal patients. However, these authors found some improvement in all but 10 to 20 per cent of the cases treated. Remissions from attacks after diphenylhydantoin sodium usually average about four months although some patients have been reported seizure-free for as long as twenty-six months. However, remissions are not uncommonly interspersed with recurrences of seizures lasting from one to three months. Compared with phenobarbital, diphenylhydantoin sodium is superior not only in the control of grand mal and psychomotor seizures but in bringing about a greater number of remissions for a longer period of time. There is increasing evidence that the combination of phenobarbital in daily doses of 90 mg. with diphenylhydantoin sodium offers the best form of therapy in most all types of epilepsy. On occasion, it becomes necessary to alter the drug therapy in the treatment of epilepsy because of side reactions or because effective results are not

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obtained. Transition from phenobarbital or the bromides to diphenylhydantoin sodium must always be made gradually and preferably with some overlapping of dosage. This procedure minimizes the danger of withdrawal symptoms due to phenobarbital or bromide (increased number of seizures) and lessens the incidence of side reactions attendant with the start of diphenylhydantoin sodium administration. Diphenylhydantoin sodium has been found by some clinical investigators to be unsatisfactory, and Peterman has returned to the use of phenobarbital. In all probability, a combination of the two as already mentioned would prove satisfactory.

The dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects if optimum results are to be expected. Such observations include the effect upon reduction of seizures and the appearance of toxic side reactions. The beginning dose for adults is 0.1 gram three times a day, and as much as twice this amount may be given if necessary. Doses greater than a total of 0.6 gram per day should never be used. For children of six years or over, the starting adult dose may be administered, but a safe upper limit is an increase to a daily dose of 0.4 gram. Children under four years of age should be given a starting dose of 30 mg. which may be increased to a daily dose of 60 mg. in two divided doses. Diphenylhydantoin sodium is strongly alkaline (pH of 11+) and hence is administered to adults and older children in the form of capsules along with at least one-half glass of water; for younger children, it is best to mix the powder with cream to avoid gastric irritation.

The chief disadvantage of diphenylhydantoin sodium is its tendency to cause *toxic side reactions* in spite of careful observation and skillful handling of dosage. Clinical reports suggest that most all patients taking the drug will exhibit one or more toxic manifestations during their course of treatment. Toxic effects involving the *Central Nervous System* are most alarming and may be manifested by ataxia, nystagmus, tremor, irritability, dizziness, staggering, or encephalopathy. In addition, psychosis, paresthesia, and the much dreaded status epilepticus have been reported. Some patients complain of *precordial* distress and electrocardiographic studies have revealed a prolongation of the PR interval and a decrease in the T wave (Finkelman and Arieff). Of the symptoms referable to the *gastro-intestinal system,* nausea, vomiting, weight loss, and gingival hyperplasia are most commonly noted. The *blood* may show an increase in basophils and/or eosinophils or a mild leucopenia may be present. Of especial interest is the increase in serum phosphatase. The toxic reactions referable to the *skin* have been variously described as a morbilliform rash accompanied by sore throat and eosinophilia, or as a purpuric or exfoliative dermatitis.

While many patients suffer from one or more toxic reactions, most untoward manifestations are more alarming than serious. One fatality associated with the use of diphenylhydantoin sodium has been reported (Dickerson). As a rule, most of the symptoms appear during the first three weeks of administration of the drug. If the dosage is reduced or discontinued temporarily, many patients may resume the use of it with-

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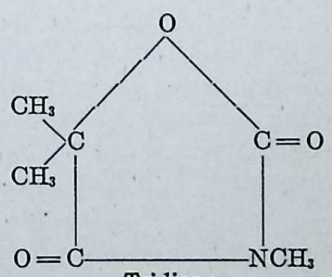
out further toxic manifestations, the one exception being exfoliative dermatitis. Of special interest is hyperplasia of the gums which was thought to be due to an alteration in the ascorbic acid content of the body. While the relationship between vitamin C and the gingival changes associated with diphenylhydantoin sodium therapy is not clear, large doses of ascorbic acid will not prevent the appearance of hyperplasia (Robinson). In spite of the high incidence of side reactions, diphenylhydantoin sodium is the most effective single preparation available for the treatment of grand mal epilepsy in adults at the present time.

Shulman has suggested the use of diphenylhydantoin sodium for the treatment of bronchial asthma in children. He found that a daily dose of 0.1 to 0.2 gram was effective in 6 out of 7 cases in which he used this drug. Of importance was his finding that personality was improved and irritability lessened. In this connection, Ross and Jackson showed that psychometric studies revealed an improvement in conduct of 50 per cent of 73 epileptic patients under treatment with diphenylhydantoin sodium. Finally, diphenylhydantoin sodium was reported useful in controlling convulsive seizures of unknown origin associated with pregnancy (Bergman). It is suggested that it might be given a trial in convulsions due to eclampsia.

Nirvanol has had some use against *chorea* in children. It is chemically related to diphenylhydantoin sodium (p. 374), but its effects are not specific for the treatment of chorea and the liability of marked toxic manifestations make its use impractical. The suggested dose is 0.3 gram daily in divided amounts. Nirvanol is not an official drug nor is it included in the N. N. R.

1. Tridione

Dilantin sodium is the most effective drug therapy against grand mal epilepsy, but neither it, phenobarbital, nor the bromides have been used very successfully to prevent petit mal attacks. Consequently, a search has been made for a chemical which would effectively control not only petit mal seizures but those of an akinetic variety as well.



Tridione

Tridione is the trade-name for 3,5,5-trimethyloxazolidine-2,4-dione. It was first described in 1938 as having hypnotic powers (Erlenmeyer).

Luton, *et al.* examined the *anticonvulsant* properties of this drug against electrically induced convulsions in mice and on convulsions produced by metrazol, picrotoxin, strychnine, cocaine, etc. These results may be briefly summarized as follows. Tridione in doses of 500 mg./Kg. had little or no effect on normal mice. Compared with dilantin sodium and phenobarbital, Tridione (in the dose mentioned) was not statistically more effective against raising the threshold

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for the production of convulsions by electrical stimulation. Phenobarbital caused some depression and ataxia, while no change in general activity was noted with dilantin sodium. Tridione, on the other hand, possessed the unusual property of being analgesic as well as anticonvulsant. However, Tridione was very effective against the convulsions produced by metrazol, strychnine, and picrotoxin. Phenobarbital was almost as effective against metrazol and strychnine convulsions, but dilantin sodium in single doses showed no anticonvulsant effect against convulsions caused by strychnine. Tridione was less effective against convulsions induced by cocaine but did exhibit some anticonvulsant action against this drug. These authors conclude that Tridione acts more like phenobarbital in that it possesses a more generalized anticonvulsant action and that it might be useful in clinical convulsive states of a subcortical origin.

The **Therapeutic Use** of Tridione was first reported by Lennox. He points out that Tridione is the most effective agent at the present time against petit mal, myoclonic and akinetic epilepsy and that dilantin sodium, phenobarbital, and bromides in order are the choice of treatment for grand mal, focal convulsions, Jacksonian and psychomotor equivalent seizures. Lennox administered Tridione to 50 patients suffering from petit mal and myoclonic and akinetic epilepsy. The usual dose of the drug was 1 to 2 grams daily, administered orally in the form of capsules, each containing 0.32 gram. He states that not much attention was paid to age in so far as dosage was concerned. These patients received Tridione over a period of fifteen months. In a few days or weeks, the minor seizures had ceased in 28 per cent, were reduced to less than one-fourth of the number in 52 per cent, and were little affected in 20 per cent. In several patients, once the seizures were stopped with Tridione, they did not return. In 10 of the 50 patients treated, grand mal was of greater significance than the petit mal attacks. Tridione was ineffective in these patients and actually made them worse.

The **Toxic Side Reactions** consist chiefly in skin rashes and an unusual sensitivity to bright light seen chiefly in adolescent children and adults. It was necessary to discontinue the drug in some patients because of skin rashes, but continued administration did not increase the photophobia, and it usually disappeared a week after medication was stopped. Of a more serious nature is the occasional occurrence of agranulocytosis and of aplastic anemia following the administration of the drug.

Tridione represents a distinct advance in the treatment of convulsive states characterized by the alternate spike and wave pattern of the electro-encephalogram. Further clinical use only will decide its proper place in psychiatric therapeutics, but it appears to hold great promise for the future.

Preparations

Diphenylhydantoinum Sodicum, diphenylhydantoin sodium ($C_{15}H_{11}N_2O_2Na$) (U. S. P.), occurs as a white odorless powder. It is freely soluble in water and soluble in alcohol. Dose, 0.1 gram.

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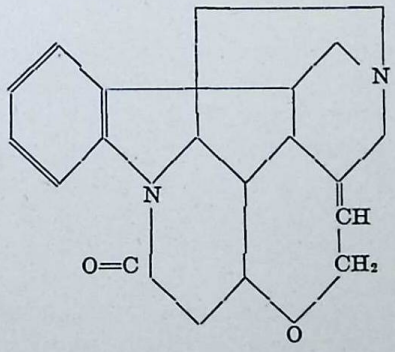
B STIMULANTS OF THE CENTRAL NERVOUS SYSTEM

I. STRYCHNINE

Strychnine is the chief alkaloid occurring in several species of Strychnos, of which the best known are *Strychnos nux vomica* and *Strychnos ignatia*. Strychnine is found chiefly in the seeds of these plants, accompanied usually by Brucine, another alkaloid, which differs from strychnine in having two methoxyl groups but which is much less active and hence of little interest pharmacologically.



Probable Formula of Strychnine (Prelog and Szpilfogel)

The alkaloids of the strychnine group have a powerful stimulant action on the central nervous system, especially on the spinal cord, throughout the vertebrate kingdom.

Symptoms.—In ordinary therapeutic doses strychnine, like other bitter substances (page 218), improves the appetite and often leads to a distinct amelioration of the subjective symptoms, the patient feeling

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stronger and more hopeful. The special senses are rendered more acute by small quantities of strychnine, for differences can be recognized between shades of color which seem identical to the normal vision; the field of vision is widened, and in certain conditions of amblyopia light is rendered much more distinct. In the same way the hearing seems to be more acute, and the sense of touch is more delicate. Some cases have been noted in which disagreeable odors were rendered pleasant by strychnine, but this would seem to be a rare idiosyncrasy. In larger doses strychnine increases the reflex movements, and the sense of touch is rendered distinctly more acute.

In cases of poisoning with strychnine, these effects are present but are not generally observed by the patient, whose first complaint is of a feeling of stiffness in the muscles of the neck and face. This is soon followed by an increased reflex reaction, so that a slight touch causes a violent movement, and even a sound or a current of air is sufficient to cause a sudden start. The increased reflex irritability is generally accompanied by some restlessness, and animals sometimes seem to make

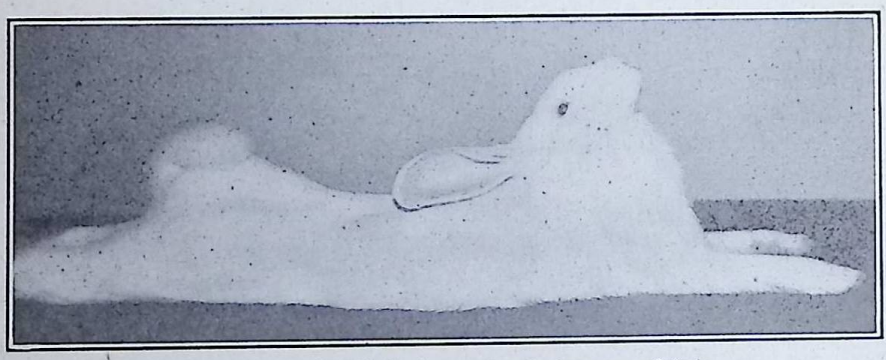

FIG. 27.—A rabbit during a strychnine convulsion.

attempts to escape from bright light. Some tremor or involuntary twitches may be observed in the limbs, and then a sudden convulsion occurs in which all the muscles of the body are involved, but in which the stronger extensor muscles generally prevail. In animals the head is drawn back, the hind limbs extended, and the trunk forms an arch with its concavity backward (opisthotonos) (Fig. 27). In man the same convulsions are seen and are accompanied by strong contraction of the face muscles, producing a hideous grin which has been called the *risus sardonicus*. The respiratory muscles are involved in the general paroxysm and the blood rapidly becomes deoxygenated, as is shown by the blue, cyanotic color of the lips and face in man. The muscles feel hard and firm at the commencement of the convulsion, but very soon a tremor may be made out, which becomes more distinct, and after a few intermittent contractions the animal sinks back in a condition of prostration. The respiration generally returns, and becomes fairly regular for a short time. Immediately after a convulsion the reflex irritability may be low, but it soon regains its former exaggerated condition and a second convulsion occurs, exactly resembling the first.

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Mammals, as a general rule, succumb after two or three convulsions, the respiration failing to return after the spasm. In some cases, however, the convulsions become shorter and the intervals of quiescence longer, the respiration becomes weak, the reflex irritability gradually lessens and the animal dies from asphyxia. In frogs, where the breathing can be dispensed with for long periods, the alternation of convulsions and periods of quiescence may continue for hours or days, but these are of the same general character as those described in mammals. After very large quantities no convulsions may occur, the animal dying almost immediately of asphyxia from paralysis of the central nervous system.

Action.—The whole character of the intoxication points to an affection of the **Central Nervous System**, and it has been found that the symptoms are unaltered when the drug is prevented from reaching the peripheral nerves and muscles. The chief symptoms arise from the spinal cord, for the convulsions are at least as well marked in frogs and mammals in which the brain has been destroyed or severed below the medulla oblongata. The intellect in man remains unclouded until the end, except for the asphyxia produced by the stoppage of the respiration; the patient is perfectly conscious of his condition, and suffers excruciating pain from the violent contractions of the muscles.

The special senses are rendered more acute by small doses of strychnine, and this is apparently due to its effects on the central nervous system in the case of touch, taste and smell, but there is reason to believe that the increase in the field of vision and the increased sensitiveness to slight differences in light are to be attributed to its acting on the cells of the retina and not to cerebral changes. For when strychnine salts are injected in the temple or applied to the conjunctiva, the sight of the corresponding eye is improved while the other remains unaffected (Filehne); if the strychnine acted centrally it could do so only by being carried to the brain by the blood, but this would affect each hemisphere equally. The affection of one eye only is explained by the strychnine diffusing through the lymph spaces, and this is said to have occurred in the case of various dyes which were applied in the same way and were then found in the retina.

Ergographic experiments have shown that small doses of strychnine augment the capacity for muscular work, and delay the onset of fatigue; this excitation phase is followed by one in which the capacity is lowered. Electrical stimulation of the motor areas of the brain is more effective under strychnine than in unpoisoned animals, but this does not necessarily indicate that the cells of these areas are acted on directly, for the same apparently increased irritability of the cortical areas is seen when the poison acts on the cord only, and it may therefore be the result of the spinal action.

The convulsions are, as has been stated, of spinal origin, in this term being included also those parts of the brain which correspond to the cord in performing simple reflex movements. It has been shown that in the frog they are reflex, that, provided no stimulus reaches the cord from without, no convulsion occurs. As has been already remarked,

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the convulsions are preceded by a stage of increased reflexes, and in fact the first convulsion is often seen to follow a stimulus, such as a blow or a loud noise. Afterwards they may seem to occur without any such impulse, but this is merely because a very slight or even imperceptible stimulus is enough to induce them. For example, a slight contraction of a muscle may induce a convulsion, as is seen very frequently in the frog, where a very slight stimulus, in itself apparently too weak to cause a convulsion, is followed by an ordinary reflex contraction, and this leads to a spasm. The absence of convulsions when external stimuli are cut off may, however, be demonstrated conclusively in various ways. Thus Poulsson found that a frog dipped in cocaine solution undergoes no convulsions after strychnine, the cocaine used being sufficient to paralyze the sensory terminations, but not to have any direct effect on the cord. Claude Bernard showed this even more conclusively by dividing all the posterior roots of the spinal nerves in the frog and then injecting strychnine, when no convulsions occurred except when the ends of the cut roots were stimulated. In mammals, however, it appears that even when all external impulses are excluded by section and degeneration of the posterior roots, convulsions still occur from strychnine; here apparently the excitability of the neurons in the cord is so extreme that they originate spasms without any impulse from without, while in the frog the advent of an external stimulus is necessary. But even in the mammal the spasms generally occur from some touch or sound or other disturbing factor.

The characteristic feature of strychnine poisoning is thus the changed response to external stimuli. In the unpoisoned animal the simple reflex movement following a stimulus is coördinated and purposive; for example, if the leg of a decapitated frog be dipped in acid it makes certain movements to withdraw the limb, and no matter how often the irritation be repeated, the same movements are produced, though it is true that if stronger acid be used the movement is more violent and a greater number of muscles are involved. In this movement certain muscles contract while their antagonists are inhibited; thus in drawing the toe away from an irritant the anterior muscles of the leg contract, while the gastrocnemius is relaxed. Under strychnine this simple reflex is stronger and is elicited by weaker irritation, and this change persists during poisoning if the external stimulus is weak and acts slowly. When a stronger or more sudden shock is applied to a poisoned animal, the response is quite different; all the muscles contract together, there being no inhibition of antagonists, and the resultant movement is thus of quite a different character; the gastrocnemius being stronger than the anterior leg muscles, the foot is extended and thrust against the irritant instead of being withdrawn from it. And not only the muscles concerned in the simple reflex, but those of the whole body are involved in the movement. This tetanic contraction of all the muscles may arise from an external stimulus which is no stronger than is required to induce a simple reflex in the unpoisoned animal. The response is the same whether the stimulus is derived from the periphery and the consequent movement is a reflex one, or from the brain. In both cases the change in the character

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of the movement arises from changes in the spinal cord, the impulse from the brain or periphery bearing its normal character, but changing its nature in passing through the cord.

It is often stated that this convulsive movement is a changed normal reflex, that under strychnine the spinal cord has lost its power of coordinating movement and can only respond to afferent impulses by efferent motor impulses to all the muscles. This is erroneous, however, for each form of response may be elicited alternately in poisoning; a weak stimulus is followed by a strong but coördinated purposive simple reflex, while a stronger one throws the body into general tetanus. This is not a development of the simple reflex, but is a totally different movement which is akin to the violent movement which occurs in normal persons and animals when a sudden unexpected touch or sound arouses them; here also the whole of the muscles contract together, and the resulting movement is determined by their relative strength; in man the powerful extensors of the trunk produce a violent straightening and the subject is said to "jump out of his chair." Strychnine lowers the threshold of the stimulus of this response, so that it is elicited by ordinary touch or weak sounds and becomes the response characteristic of the poisoning.

When an external stimulus is sufficient to cause this convulsive movement in a poisoned animal, the contraction is always maximal; a stronger stimulus produces no greater effect.

As regards the locus of action of strychnine in the cord, the experiments of Dusser de Barenne indicate that the drug acts on the cells of both the sensory, and motor regions. It is this action on both areas which leads to the characteristic response, rather than an action on the sensory elements alone or on the synapses of the neurons intercolated between the posterior root (sensory) and the cells of the anterior horn (motor) as was formerly believed.

An impulse travelling up a nerve in an unpoisoned frog reaches the cord and may there pass through a number of paths and in each is subjected to various influences, so that it arouses different motor cells to different degrees of activity, or actually inhibits the activity of some of them; in this way a coördinated movement follows. Under strychnine these influences, which may be figured as varying resistances in the different paths, disappear, and the impulse passes untrammeled along all available paths and reaches the motor cells in much greater force than normally and thus arouses a more powerful reaction from them and a correspondingly strong muscular contraction. But the resistance in the different paths is essential to coördinate the movement and the increased muscular contraction is thus no longer coördinated, all the muscles contracting together and the character of the movement being determined by their relative strength. The action of strychnine may thus be explained by supposing that it removes resistances to the passages of impulses through the spinal cord and thus extends the area on which an impulse acts, and also liberates it from the normal coördinating influences.

It must be remarked that while the resistance is much reduced, it

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is not entirely removed, and the ordinary path is still somewhat more easily traversed than the others, for weak irritation causes an ordinary reflex response in the frog, while a slightly stronger stimulus throws it into opisthotonos. In this condition a whole series of discharges occurs of longer duration than the simple reflex, and this without any further impulses reaching the cord either from without or from the muscles and joints involved in the movement; for when all movement is excluded by curare, the electrical changes can be observed in the cord corresponding to the muscular spasms in the convulsions.

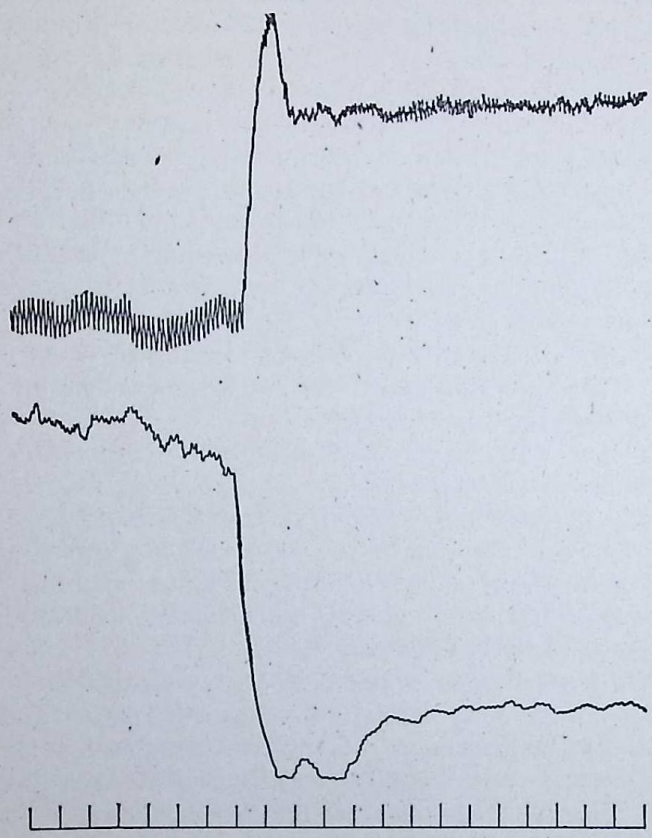

FIG. 28.—Tracings of the blood-pressure (upper) and intestinal volume (lower) from a curarized cat, showing the effect of the intravenous injection of a dose of strychnine sufficient to cause spasms in an uncurarized animal. The blood-pressure rises, while the mesenteric vessels are contracted from spasm of the vasomotor center (Bayliss).

Sherrington found that a stimulus which normally produces reflex contraction of a muscle with inhibition of the opposing muscle may, in an animal under strychnine, produce a contraction of both muscles; that strychnine apparently changes an inhibitory into a motor response ("strychnine reversal"). He later suggested, as another possible explanation of the phenomenon, that the apparent reversal might really be due to the exaggeration of a masked motor component in the inhibitory response. The correctness of the latter assumption was shown by Bremer, who found that strychnine only amplifies the motor element, more or less apparent, in the inhibitory component of a reflex response.

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Creed and Hertz have shown that the relaxation of a diaphragm slip, evoked by inflation of the lungs, is never replaced by contraction as a result of administering strychnine, and they support Bremer's conclusion that the action of strychnine is not to convert central inhibition into central excitation but to facilitate the passage of excitatory processes through reflex arcs.

Besides the spinal cord, all other regions in which simple reflexes can be produced, are affected by strychnine. Thus the medullary centers are thrown into the same condition, and their responses to stimuli are equally exaggerated; but they are in constant receipt of impulses, and strychnine, by increasing the efficiency of these, augments the tone of the medulla oblongata when it is given in small quantities.

Artificial respiration has been shown to delay the onset of convulsions in animals, but it is still an open question whether this is due to the better aeration of the blood (Osterwald) or to the effects of the mechanical movements (Gies and Meltzer).

The stimulation of the spinal cord by strychnine is followed by depression and paralysis. Even during the first stage the stimulation is mixed with depression, for though a more violent response is induced by a sensory stimulus, this cannot be repeated so often as in the normal frog, as the cord becomes fatigued more readily. The sensory part of the spinal cord seems to be paralyzed somewhat earlier than the motor cells, but these also lose their irritability after a time and no further movement can be elicited either by reflex or by direct stimulation of the cord.

Strychnine seems to have no direct action on the voluntary **Muscles**; it is stated that minute quantities increase their tone, that is, render them more tense, so that they are prepared for immediate contraction, but this is due to action on the cord and not on the muscle fibers.

The **Terminations of the Motor Nerves** are paralyzed by large doses of strychnine in the same way as by curare. This effect is scarcely seen in mammals, as central paralysis always precedes it and destroys life, but in some species of frogs the nerve ends are paralyzed before the central nervous system. This paralysis is not due to the exhaustion of the nerve ends through the tetanus, but is a direct action on the terminations, although the exhaustion may contribute to the result.

The **Respiration** is quickened by small quantities of strychnine, especially when the center is depressed by the previous administration of a narcotic. However, to be really effective as a respiratory stimulant so as to increase the respiratory volume, the dose of strychnine must approach very close to the convulsive dose. From the use of adequate doses of strychnine the change in respiratory volume is mainly due to the great increase in the depth of the respiratory movements and not so much to a change in rate. During strychnine convulsions the breathing is arrested by the violent contractions of the diaphragm and the other respiratory muscles, but during the intermissions it continues fairly regular. After one or two spasms it often fails to be reinstated, and the animal dies of asphyxia; in other experiments it undergoes a

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gradual diminution in rate and strength, and eventually ceases from gradual paralysis of the center.

The **Heart** is not directly affected by strychnine in mammals, though it is sometimes slightly slowed by stimulation of the inhibitory center. During and after a convulsion it may be accelerated, as in violent exertion from any cause. Very large quantities slow and weaken the frog's heart.

The **Vasomotor Centers** in the medulla oblongata and the cord are often stimulated by small quantities, so that the splanchnic vessels are constricted, while the cutaneous and perhaps the muscular vessels tend to dilate from stimulation of the vasodilator center. The blood is thus deflected to some extent from the abdominal organs to the skin and limbs, as well as to the heart, lungs, and brain which have little or no vaso-constrictor supply. Stimulation of the depressor nerve causes a rise of blood-pressure after strychnine, due to the presence of pressor elements in the nerve stimulated. Langley showed that reflex vasomotor effects in the spinal animal are markedly exaggerated by strychnine.

During the convulsions the blood-pressure is raised to an extreme height, partly owing to the activity of the vasomotor center and perhaps partly from the blood being pressed out of the abdominal organs and the muscles by the violent contractions. Immediately after a convulsion the blood-pressure falls, probably from the exhaustion of the center.

Strychnine stimulates the output from the adrenal glands and may thus indirectly produce sympathomimetic effects on the circulation and on other organs.

In the **Alimentary Tract**, strychnine has the same action as any other bitter substance, and it produces a flow of saliva and increased appetite if taken before meals. (See Stomachic Bitters, page 218.) It seems to be absorbed from the intestine mainly. After absorption it was thought to increase the movements of the bowel from some action on the muscle or on the ganglionic plexus in the bowel wall, but careful studies carried out on the human patient, by means of a balloon placed in the lumen of the intestine and peristalsis thus recorded, have shown that any change which is produced by the small doses usually employed is inconsequential and could readily be obtained by other less dangerous drugs.

Metabolism.—Strychnine produces an enormous activity of the muscles, and, therefore, increases very greatly the consumption of oxygen and the output of carbonic acid. This is accompanied by an increased formation of heat, which would lead to a rise in the temperature of the body were it not counteracted by an equal or even greater increase in its dissipation through the skin. As a result the temperature is generally lowered in rabbits, while it sometimes rises slightly in dogs and cats. The skin temperature, on the other hand, rises considerably because more blood flows through it than usual.

Glycosuria occurs in frogs and in young mammals, and the glycogen of the liver and muscles disappears in most animals under strychnine. The glycosuria is probably secondary to the liberation of epinephrine from the adrenal medulla; the depletion of the glycogen from the liver

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and muscle results from the increased muscular movement and the disturbance of the respiration.

Strychnine is absorbed rapidly and is distributed equally in the red corpuscles and plasma of the blood. In man from 10 to 20 per cent of that ingested appears in the urine, in which the reaction begins usually within an hour and may remain three or more days. The rest of the alkaloid is taken up by the liver and undergoes oxidation. No marked tolerance is developed for strychnine, even after very prolonged administration; indeed, increased susceptibility may result.

The action of strychnine is almost identical throughout the vertebrate kingdom. Man is more susceptible than other mammals, and young animals are more refractory than adults, perhaps owing to the less developed condition of the central nervous system. It has been found also that females are much more susceptible to strychnine than males. At least this is true in the case of white rats. The domestic fowl tolerates comparatively large quantities without symptoms. The convulsant action is seen in some of the higher invertebrates; in the lower it induces paralysis only.

Brucine, the second alkaloid of nux vomica, resembles strychnine closely in action but is much weaker, from 30 to 80 times as large a dose being required to produce the same effect. It differs from strychnine also in possessing a more powerful action on the nerve terminations in voluntary muscle, especially in some species of frog. Strychnine and brucine are present in nux vomica in almost equal proportions.

A third alkaloid, Vomicine, has been described, which produces clonic convulsions differing from those produced by strychnine and apparently due to an action on the cerebrum.

Therapeutic Uses.—Strychnine was formerly used widely for a variety of conditions but its importance as a therapeutic agent is negligible and many of its applications are irrational. It is administered in the form of the hydrochloride, nitrate or sulfate of strychnine; as the Tincture of Nux Vomica which contains from 1.1 to 1.2 mg. of strychnine per cubic centimeter; and as the Extract of Nux Vomica which contains 7.5 per cent strychnine. The dose of the strychnine salts is 1 to 2 mg.; of the Tincture, 0.6 to 1 cc. and of the Extract, 15 mg.

Strychnine was formerly used largely for its local action on the digestive organs as a *stomachic bitter*, and was prescribed in the form of the tincture or the extract for this purpose, as in this way it is less rapidly absorbed than when given as an alkaloidal salt. It may be combined with the cinchona preparations or with one of the simple bitters.

Small quantities of strychnine are also used as a tonic in many ill-defined conditions of weakness, cachexia, and *"want of tone"* generally. It is questionable, however, if its slight action on the nervous system in increasing the irritability of the cord can be of any therapeutic value.

As a *stimulant to the central nervous system* strychnine has found wide application in almost every form of paralysis, and in many neurological disorders but it is doubtful if any effects are elicited in doses which are not toxic.

Strychnine has been used as a *respiratory stimulant* in some pulmonary conditions in which it is desirable to increase the respiration or to provoke coughing but effective doses cannot be given with safety in

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these conditions. However, this is possible in failure of the respiration during anesthesia, or still more frequently, in cases of poisoning from the soporifics, particularly the barbiturates, and it is certainly more likely to be beneficial than a number of other drugs suggested for this purpose. In other forms of poisoning in which the respiratory center is in danger, strychnine may also be of service. In such cases it should be injected hypodermically.

In *amaurosis* or amblyopia unassociated with atrophy of the optic nerve, and even in commencing atrophy, strychnine is claimed to improve the vision. In many cases it fails to produce any benefit, and the exact conditions in which improvement can be looked for are unknown.

Strychnine has been used in heart disease, but all exact observations agree that it has no beneficial action (Parkinson and Rowlands). In weakness of the circulation from *inefficiency of the vasomotor center* it may act, but it is of no value in the treatment of the low blood-pressure of shock.

Poisoning.—Strychnine poisoning is most commonly observed in children who mistake the drug for candy. The treatment of strychnine poisoning is directed to abolishing the convulsions and protecting the medullary centers from excessive stimulation. This is best accomplished by the intravenous administration of a suitable barbiturate (the sodium salts of pentobarbital, phenobarbital, or amytal) in an amount (usually between 0.3 and 1 gram) necessary to induce sufficient depression to abolish the convulsions but not to depress respiration or blood-pressure.

After the convulsions have been abolished, any of the drug remaining in the stomach should be removed by gastric lavage.

The patient should be protected against all external stimuli by being placed in a dark, quiet room and barbiturate administered again if muscle twitchings and signs of increased reflex irritability appear.

If barbiturates are not available chloroform may be used temporarily to control the convulsions and allow lavage of the stomach.

Preparations

U. S. P.

Nux Vomica, the dried ripe seeds of Strychnos nux vomica, containing not less than 2.5 per cent of the alkaloids of nux vomica.

Strychninæ Sulfas (soluble about 1 in 35 of water). Dose, 2 mg.

Tabellæ Strychninæ Sulfatis, tablets of strychnine sulfate. Dose, 2 mg.

Tinctura Nucis Vomicæ (about 0.1 per cent of strychnine). Dose, 1 cc.

B. P.

Extractum Nucis Vomicæ Liquidum (1.5 per cent of strychnine). Dose, 0.06 to 0.2 mil. (1 to 3 min.).

Extractum Nucis Vomicæ Siccum (5 per cent of strychnine). Dose, 0.015 to 0.06 gram.

Liquor Strychninæ Hydrochloridi (1 per cent of strychnine hydrochloride). Dose, 0.2 to 0.8 mil.

Nux Vomica, the seeds of Strychnos nux vomica, containing not less than 1.2 per cent of strychnine.

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NUX VOMICA PULVERATA, standardized to contain 1.2 per cent of strychnine. Dose, 0.06 to 0.25 gram.

STRYCHNINÆ HYDROCHLORIDUM (soluble in water about 1 in 40). Dose, 0.002 to 0.008 gram.

SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA, "Easton's Syrup" (0.025 per cent of strychnine). Dose, 2 to 4 mil.

TINCTURA NUCIS VOMICÆ (0.125 per cent of strychnine). Dose, 0.6 to 2 mil.

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II. PICROTOXIN

Picrotoxin is the best known member of a group of convulsive poisons, which resemble each other very closely in action. It has the empirical formula ($C_{30}H_{34}O_{13}$); and may be broken up into picrotoxinin ($C_{15}H_{16}O_6$), which resembles it in its effects on animals, and picrotin ($C_{15}H_{18}O_7$), which is inactive. Picrotoxin is obtained from the berries of *Cocculus indicus*, a shrub found in the East Indies.

Other poisons resembling picrotoxin are *Cicutoxin*, derived from the Cicuta virosa, or water hemlock, and probably from other species of Cicuta, "*nanthotoxin*, the active principle of Œnanthe crocata, water dropwort, or dead tongue, and *Coriamyrtin*, which occurs in several species of Coriaria, of which the best known is the Coriaria myrtifolia or currier's sumach; *Tutin*, the active principle of the toot or tutu poison of New Zealand, is obtained from other species of coriaria. Some of these bodies are glucosides. *Camphor* and some other volatile oil derivatives, notably the *Thujon* of absinthe, also resemble picrotoxin in their effects, and the same is true of two alkaloids *Samandarine* and *Samandaridine* isolated by Faust from the skin of the newt. Lastly, some poisonous substances inducing symptoms like those of picrotoxin have been formed by the decomposition of the glucosides of the digitalis series.

Symptoms.—The symptoms, which are often somewhat late in appearing, are very similar in all classes of vertebrates. In man vomiting is not infrequently observed, or the first symptoms may be salivation, acceleration of the respiration, and some slowness and palpitation of the heart. Stupor and unconsciousness follow and then a series of powerful convulsions, which, commencing in tonic spasms, soon change to clonic movements of the limbs, which are alternately extended and flexed in contrast with the prolonged contraction under strychnine. The respiration is interrupted during these spasms, but is reinstated during the intervals of quiet and collapse which follow them. The convulsions

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return after a short pause, and this alteration of spasm and quiet may continue for some time, although the respiration often fails to return after one of the spasms, and fatal asphyxia results.

Similar effects are observed in the lower mammals. After a preliminary stage in which twitching of the muscles and vomiting often occur, and in which the respiration is accelerated while the pulse is slow, a violent emprosthotonic convulsion sets in, but soon changes to clonic movements; these may last for some time, but eventually become weaker and give place to a condition of quiet and depression. An increase in the reflex excitability is noticeable during this interval; the animal is easily startled and occasional twitching of the muscles may be observed. Very soon a second convulsion sets in, and this may be fatal from asphyxia, but the symptoms often continue for an hour or more, violent spasms alternating with periods of depression and collapse. In the frog, clonic convulsions are also the chief feature of the intoxication. Very often the animal becomes distended with air during the convulsions, and gives a curious cry in releasing it. The heart is always slowed and may cease to beat altogether for a time.

Action.—The clonic convulsions of picrotoxin poisoning are different from those of strychnine and other similar bodies, which induce prolonged tonic convulsions, and it was early surmised that the members of this series act on a different part of the **Central Nervous System.** In the fish, convulsions arise from picrotoxin after all the nervous system has been removed except the spinal cord. In the frog they persist when all of the brain above the medulla oblongata has been removed, although they are weaker after destruction of the optic lobes; on the other hand, they lose their typical character when the medulla oblongata is removed. In a frog ten times as much picrotoxin is required to produce convulsions after ablation of the mid-brain as is necessary when the mid-brain is intact. In mammals, the convulsions are less typical when the cerebral hemispheres are removed and disappear when the pons is destroyed. The seat of action thus seems to move upward as the higher parts of the central nervous system become more developed, the chief effects arising from the spinal cord and medulla and optic lobes in the frog and from the cerebrum and mid-brain in mammals. It is possible that in man the cerebrum is even more involved in the action than in the lower mammals. In Toot poisoning in man, it is often observed that a confused mental condition is present and that the memory is impaired after the attack and for some days later.

The stimulation of the medulla is seen in the acceleration of the respiration, in the slow pulse, which is due to inhibitory action, in a very marked rise of the blood-pressure, and in the vomiting and salivation. In many animals the reflexes are found to be increased when the medulla is severed from the cord, and this indicates that the spinal cord is also more excitable than normally. Grünwald suggests that the centers controlling the cranial and sacral autonomic nerves are especially susceptible to the action of these poisons.

Duff and Dille have studied the detoxification of picrotoxin in rabbits and showed that in this animal at least the drug is rendered inactive quite rapidly. For example, he found that it was possible to inject repeatedly convulsive doses of picrotoxin at intervals of an hour and a half or two hours with survival of the animal. Traces of a convulsive substance were found in the urine, indicating that the large portion of the poison was disposed of in the body in some other manner than through the kidney. Like other convulsive poisons, it tends to lower the temperature when it is given in quantities insufficient to cause convulsions.

The convulsions of picrotoxin and its allies disappear when chloroform or chloral is administered and in rats are abolished by stramonium. On the other hand, the respiration, weakened by narcotic poisons such as chloral, is accelerated by picrotoxin, the blood-pressure rises, and the sleep is less prolonged. Marshall and his co-workers found that picrotoxin was effective as a stimulant to respiration which had been depressed by various means, such as by carotid sinus inactivation and by drugs such as chlorbutanol or avertin. It was less effective against urethane and of no value against ethyl alcohol. In normal

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unanesthetized animals it was effective only when given in convulsive doses, but in anesthetized animals it was active in non-convulsive amounts and according to the view of these workers its action upon the depressed respiration is probably due to the lessening of the depth of narcosis, bringing the animal to a more nearly normal condition. Krantz, Carr and Beck made a study of oxygen consumption during the period of the antagonistic action of picrotoxin against pentobarbital and found that in rats picrotoxin significantly antagonized the depressed oxygen consumption due to the barbiturate, but that it did not accelerate oxygen consumption which had not been previously depressed. They do not believe that the antidotal action of the picrotoxin is associated with the increased oxygen consumption but that it is due to its convulsive action, reducing the depth of the narcosis. Animals and persons are not awakened at once from narcosis by picrotoxin, but coriamyrtin has this effect.

Therapeutic Uses.—Picrotoxin is used in therapeutics as an antidote in barbiturate poisoning and has been used rather extensively following the studies by Maloney, Fitch and Tatum. In these and other studies it was shown quite definitely that animals which had been given doses of the barbiturates, which under ordinary conditions would surely have proved fatal, recovered when treated with picrotoxin. It is administered in doses of 1 to 3 mg. intravenously or 3 to 6 mg. intramuscularly every fifteen minutes until the desired response is obtained, or it may be given continuously at a rate of 1 to 2 mg. per minute until the corneal, swallowing or other reflexes appear. Artificial respiration, an open airway, oxygen, gastric lavage and intravenous fluids should be employed concurrently with the picrotoxin therapy.

An interesting sidelight which has been encountered in connection with this use of picrotoxin is the large doses of the substance which such comatose patients will tolerate. In the normal animal, and probably also in the human patient, it is quite toxic, yet to the patient in coma relatively enormous doses have been given. Cases have been reported of patients receiving between 200 and 300 mg. of picrotoxin in from twenty-four to forty-eight hours. One patient received a total of 2.134 grams in eight days. It will be seen that each case is a problem in itself and as such requires careful individual study.

The safety of the large doses which have been employed is rather unusual and would point to a rapid detoxification of the drug in the body, which view would be supported by the study of the fate of picrotoxin in the rabbit.

Preparations

U. S. P.

Picrotoxinum, picrotoxin, shining crystals or microcrystalline powder, sparingly soluble in water. Dose, 2 mg.

Injectio Picrotoxini, a sterile solution of picrotoxin in isotonic solution of sodium chloride. Dose, 2 mg. or more intravenously depending upon the severity of the barbiturate poisoning.

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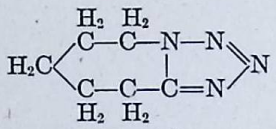
III. OTHER ANALEPTICS

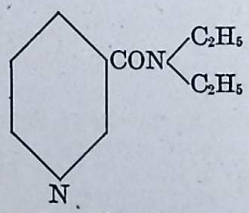
Metrazol. (Leptazol), pentamethylentetrazol, was introduced by the trade name of "Cardiazol." It was found by Hildebrandt (1926) to produce epileptiform convulsions in frogs and mammals with large doses, and with small doses stimulation of the respiration and augmentation and acceleration of the heart when that organ was previously weakened by chloroform or other depressants. It has been recommended as a remedy for circulatory failure as an improved substitute for camphor but other investigations have found no evidence, pharmacological or clinical, for this effect, unless the drug be used in convulsive doses. The evidence that it stimulates the respiratory and vasomotor centers is in keeping with its undoubted effect in stimulating other areas of the central nervous system and its analeptic action. However, it is a very uncertain respiratory stimulant in conditions of depressed respiration in animals in which other stimulants are effective.



Metrazol

The principal use of metrazol has been in the treatment of psychiatric disorders by convulsive therapy. As shown by Meduna the convulsions induced by metrazol induced more or less the same response in these cases as did those induced by insulin. More recently electric shock therapy has to some extent displaced both of these drugs in psychiatric practice.

Metrazol is a water soluble white powder which may be administered intramuscularly, subcutaneously, intravenously or orally in doses of 0.1 to 0.3 gram, as required.



Nikethamide

Nikethamide (Coramine).—Another synthetic compound of this group was introduced under the trade name of "Coramine." Chemically it is pyridine-β-carboxylic acid diethylamide, and is the diethylamide of nicotinic acid. It is a yellowish liquid, freely miscible with water. Faust (1925) found that it produced an increase in the respiratory rate with rise of blood-pressure, (by reflex stimulation from the carotid body). Toxic doses produced excitement, tremors, and finally convulsions. It has been widely used as a stimulant for the respiration and circulation, and has been specially recommended for cases of overdosage with avertin, morphine or other narcotics. The evidence goes to show that it is a useful respiratory stimulant and that the beneficial effect on the circula-

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tion when it occurs is due partly to the stimulation of the vasomotor center and possibly other reflex centers and is partly secondary to the improved respiration. There is no evidence to indicate that the drug has a direct stimulating effect on the myocardium or coronary vessels.

Because of its analeptic action, nikethamide is used in acute respiratory depression of anesthesia, alcoholic intoxication, and overdosage with hypnotics. The value of different analeptics in narcotic poisoning varies considerably with the particular narcotic involved.

Nikethamide is used in a 25 per cent aqueous solution. In emergencies it must be administered intravenously in doses of 1 to 5 cc. as required. It is rapidly inactivated in the blood stream. When doses larger than 3 cc. are given, the administration should be slow with close observation of the patient since large doses may induce convulsions and death from respiratory failure.

PREPARATIONS

B. P.

LEPTAZOLUM, leptazol, $CH_2(CH_2)_4C{:}N{:}N{:}N.N$. Dose, 0.05 to 0.1 gram.

INJECTIO LEPTAZOLI, injection of leptazol. Dose, subcutaneously, 0.5 to 1 mil.; intravenously as a convulsant, 2 to 5 mil. increasing to 12 mil.

NIKETHAMIDUM, nikethamide, $CH{:}CH{\cdot}CH{:}N{\cdot}CH{:}C.CON(C_2H_5)_2$, is the diethylamide of pyridine-β-carboxylic acid. Dose, 0.2 to 0.5 gram; intravenously as a stimulant, 0.5 to 1.25 gram.

INJECTIO NIKETHAMIDI, injection of nikethamide. Dose, subcutaneously or intramuscularly, 1 to 4 mil.; intravenously as a convulsant, 5 to 16 mil.

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IV. THE XANTHINES

Caffeine, Theobromine and Theophylline

In a number of plants used in different parts of the world to form beverages and condiments, there are found the xanthine compounds, *Caffeine, Theobromine* and *Theophylline* (*Theocin*), which are also employed in therapeutics, and have, therefore, acquired a double importance as drugs and as articles of diet. The widespread use of preparations of these by uncivilized peoples is a curious and unexplained fact, especially as they possess neither peculiar taste nor odor to guide in the selection of the plants in which they exist. Besides, caffeine and its allies in moderate quantities induce no marked symptoms, such as follow the use of alcohol, opium or hashish and explain their use among widely separated peoples. On the contrary, the only effects to be observed are a brightening of the intellectual faculties and an increased

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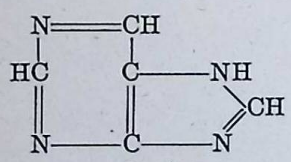
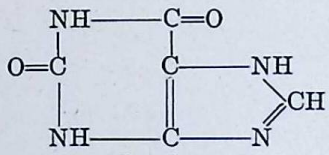
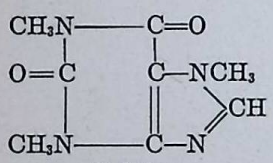
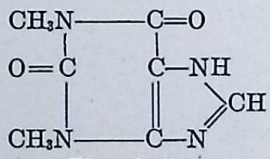
capacity for mental and physical work. Coffee, the use of which is derived from the Arabians, is the berry of Coffea Arabica and contains caffeine; tea, the leaves of Thea Chinensis, contains caffeine along with theophylline. Cacao, cocoa, or chocolate is derived from the seeds of Theobroma cacao, a tree indigenous in Brazil and Central America, and contains theobromine. In central Africa, the Cola or Kola nut (Sterculia acuminata) is used by the natives, and contains caffeine with small quantities of theobromine. In Brazil, Guarana paste is formed from the seeds of Paullinia sorbilis, and contains caffeine and theobromine, while in the Argentine Republic, Yerba Mate or Paraguay tea (Ilex Paraguayensis) is used to form a beverage which contains a small quantity of caffeine. Another species of Ilex is met with in Virginia and Carolina under the name of Apalache tea or Youpon, and also contains caffeine.

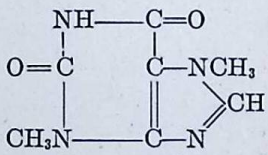
Caffeine, theobromine and theophylline are purine derivatives closely related to the xanthine bodies found in the urine and tissues of animals. As seen in the accompanying formulæ:


Purine


Xanthine


Caffeine


Theophylline


Theobromine

xanthine is 2:6 dioxypurine; caffeine is 1:3:7 trimethylxanthine; theobromine is 3:7 dimethylxanthine, and theophylline is 1:3 dimethylxanthine.

Action.—These all resemble each other in most points of their pharmacological action, but they differ markedly in the relative intensity of their action on various functions. Thus caffeine is the most potent central nervous system stimulant of the group; theobromine exerts the greatest action on the muscles; and theophylline is the most effective diuretic and coronary dilator. Theobromine has comparatively little effect on the central nervous system, while theophylline has no action on the muscles.

Central Nervous System.—In man, caffeine stimulates the central nervous system, in particular that part associated with the psychical functions. The ideas become clearer, thought flows more easily and rapidly, and fatigue and drowsiness disappear. Not infrequently, however, connected thought is rendered more difficult, for impressions follow each other so rapidly that the attention is distracted, and it requires more and more effort to limit it to a single object. If the quantity ingested is small, however, the results are of distinct benefit

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in intellectual work. The capacity for physical exertion is also augmented, as has been demonstrated repeatedly by soldiers on the march, and more recently by more exact experiments with the ergograph. However, recently acquired motor skill requiring muscular coördination may be adversely affected. The stimulation of the higher nervous centers is often manifested in the insomnia and restlessness which in many people follow indulgence in coffee or tea late at night. Kraepelin showed that both tea and coffee facilitate the reception of sensory impressions and also the association of ideas, especially in fatigue, while the transformation of intellectual conceptions into actual movements is retarded. This he regarded as due to stimulation of the highest or controlling functions of the brain, caffeine acting on the same parts as are first affected by alcohol and the methane derivatives, but altering them in the opposite direction. The effect of caffeine on the acuteness of the senses has been demonstrated by the greater accuracy of touch under its influence.

Large quantities of caffeine often cause headache and some confusion and in rare cases of special susceptibility a mild form of delirium may be elicited, or noises in the ears and flashes of light may indicate derangement of the special senses. The pulse is quickened, and occasionally palpitation and uneasiness in the region of the heart are complained of. Convulsive movements of the muscles of the hand, and tremor in different parts of the body have also been recorded in some cases. These effects are induced only with difficulty in habitual drinkers of tea or coffee, so that the continued administration of small quantities of caffeine evidently gives rise to some tolerance.

In the lower mammals the injection of large quantities of caffeine is followed by symptoms closely resembling those induced by strychnine. The reflex irritability is remarkably increased, the lightest touch being followed by powerful contraction of almost all the muscles of the body. After a time these contractions occur without any apparent stimulus, and culminate in tonic convulsions which last for several seconds. During these, the respiration ceases because the respiratory muscles are involved in the spasm, and occasionally it fails to be reinstated when the convulsions pass off. In other instances the spasms become weaker and occur at longer intervals; the respiration diminishes in frequency and depth and eventually ceases.

The symptoms induced by caffeine in the lower mammals are due for the most part to its acting on the spinal cord in the same way as strychnine, though small doses may act on the brain, for they often elicit restlessness and timidity without any marked change in the reflex excitability. The centers in the medulla oblongata are also involved in the effects, as is indicated by acceleration of the breathing and occasionally by some slowness of the pulse from action on the vagus center.

On comparing the effects of caffeine and strychnine on the central nervous system, it will be found that while there is a general similarity in their action, the latter causes more marked stimulation of the lower divisions and has less action on the cerebrum in mammals and man. They both produce a general increase in the activity of nerve cells, but

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caffeine acts more on the psychical, strychnine more on the reflex, functions. Theophylline resembles caffeine in its action on the central nervous system, while theobromine induces few or no symptoms of stimulation.

Muscular Action.—When a few drops of caffeine solution are injected into the leg of a frog there follows a peculiar stiffness and hardness in the muscles around the point of injection, which slowly spreads to other parts of the body and induces the appearance of rigor mortis. The same effect is observed when teased muscle fibers are subjected to a caffeine solution under a high-power microscope. The fibers contract, become white and opaque, and look stiff and inflexible; the transverse striæ disappear, while the longitudinal become more easily visible. This appearance is due to the death and rigor mortis of the fibers, in which the myogen is apparently formed into myogen-fibrin; the same change occurs when caffeine is added to myogen in the test-tube.

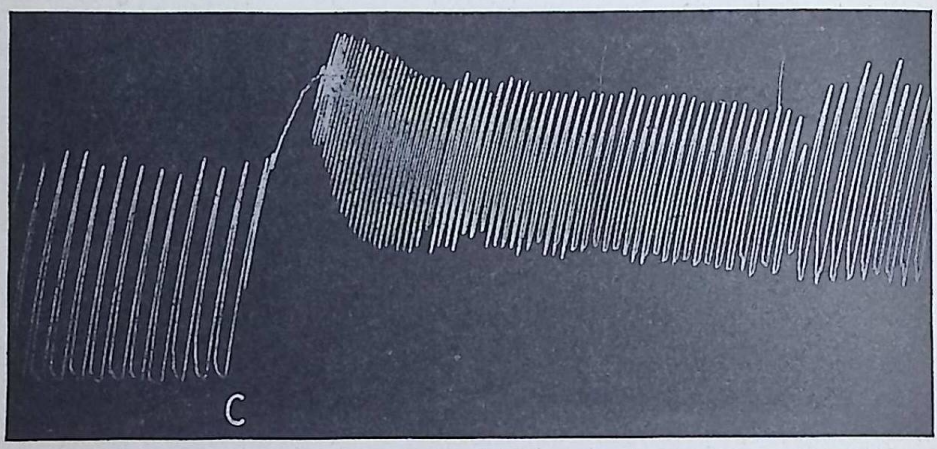

FIG. 29.—Respiration of a rabbit which had been slowed by morphine. At *C*, caffeine was injected intravenously and the respiration was at once greatly accelerated and moved toward the inspiratory position.

In small quantities caffeine increases the irritability of muscle as well as its absolute strength and extensibility; that is, the muscle contracts on a weaker stimulus and against a greater load than it does normally. The amount of work done before fatigue sets in is also increased, unless when large quantities are applied, when the capacity for work is lessened; and with the first appearance of rigor it ceases to react to stimuli altogether. Caffeine augments the amplitude of contraction of muscles stimulated by acetylcholine by lowering the excitatory threshold to this drug. It also augments the action of neostigmine and has a decurarizing effect. The universally recognized effect of tea and coffee in increasing the capacity for physical work and in relieving fatigue has generally been regarded as due to changes in the nerve cells, and it does not seem likely that the action on the muscle contributes to it; for theobromine, which acts strongly on muscle while it has little effect on the central nervous system, fails to remove fatigue and to increase working capacity in the same degree as caffeine.

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The xanthines also act on smooth muscle. Theophylline relieves the spasm of the biliary tract and is an effective broncho-dilator in asthma.

Circulation.—When caffeine is injected in large quantities intravenously in animals, the heart is accelerated considerably without any significant change in the extent of systole and diastole. The acceleration is not dependent on changes in the regulating nerves of the heart, but arises from a direct stimulating action on the cardiac muscle, and especially on that part from which the rhythm originates. Vagus stimulation has less effect than usual, but this is due to increased irritability of the heart and not to partial paralysis of the nerve ends. A similar acceleration is induced by caffeine after division of both accelerator and vagus nerves and after the paralysis of the inhibitory terminations by atropine. Still larger quantities of caffeine injected intravenously in mammals cause weakness and irregularity of the heart. The amounts used in therapeutics in man seem insufficient to induce either the acceleration or the subsequent irregularity observed in animals. The acceleration of the heart is not always accompanied by an increase in cardiac output, for the contractions may follow each other so quickly that there is not sufficient interval for the inflow of blood.

The blood-pressure under these large intravenous injections in animals often rises to some extent, but not infrequently shows little alteration, and the increase in the blood-pressure is rarely significant. Caffeine tends to stimulate the vasomotor center in the medulla, and this would raise the blood-pressure, were it not for a simultaneous widening of the vessels through a direct action on the walls; this neutralizes in large part the central action on the circulation, so that the blood-pressure shows only slight changes (Sollmann and Pilcher). When very large quantities weaken the heart, the blood-pressure falls to a considerable extent, but if convulsions supervene it may again rise.

When caffeine or theobromine or theophylline is perfused through the surviving heart, the coronary arteries are dilated, and this has led to the use of these drugs in conditions in which narrowing of these vessels is supposed to be present. A similar effect is observed in the intact unanesthetized animal in which the coronary flow may be doubled following xanthine medication (Essex, *et al.*). It has also been claimed that the xanthines facilitate the establishment of the collateral circulation in dogs with experimental myocardial infarction but the available data on this point are conflicting.

In the normal human small doses of caffeine are without effect on the cardiovascular system. Larger doses (0.5 to 1 gram) cause no change in pulse rate but increase the cardiac output slightly. In some individuals in whom subjective nervous effects follow the ingestion of caffeine this is accompanied by pronounced elevations in the pulse rate, blood-pressure and cardiac output (Grollman). These effects are probably secondary to the stimulation of the central nervous system. More striking effects are elicited following the injection of theophylline compounds (Starr, *et al.*).

Metabolism.—Caffeine in doses of 0.5 to 1 gram causes an increase in oxygen consumption of 10 to 35 per cent in the normal human. This

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may account for the observed rise in body temperature which is, however, comparatively insignificant (0.5° to 1° C.) and is seen only in cases in which an almost poisonous dose has been used.

The **Respiration** is quickened by caffeine, owing to a stimulant action on the medullary center. This is seen in the improvement of the respiration in cases of dangerous poisoning with alcohol, opium and other drugs which prove fatal by depressing the center, but is much less marked in normal animals. The quicker respiration is often more shallow than before the administration of caffeine, but the total air breathed is increased and the blood is better aerated; the lessened content of carbon dioxide in the blood causes the breathing to be shallower through lessening the stimulus to the respiratory center. The action of caffeine on the center is thus diametrically opposed to that of morphine.

The **Alimentary Tract** is not often affected by theobromine and caffeine, but after either of them discomfort and loss of appetite are sometimes complained of, probably owing to changes in the gastric mucous membrane. These are much more marked after even small doses of theophylline, which has been found to produce small hemorrhages and erosions in the stomach, both in man and animals (Allard). This action of caffeine on the gastric mucosa has also been considered as a possible mechanism of the causation of gastric ulcer in man (Ivy). This stimulation of the gastric secretion of hydrochloric acid by caffeine is particularly prolonged and excessive in patients with ulcer (Musick, *et al.*).

Kidney.—It is an everyday experience that strong coffee or tea increases the urine to a much greater extent than the same amount of water, and this has been shown to be due to the caffeine contained in these beverages. Caffeine injected intravenously in the rabbit has a similar diuretic effect, though there is often a short preliminary period in which the secretion is actually diminished; this is especially marked when the injection is made rapidly, and may arise from circulatory changes or perhaps from the action of an overwhelming dose on the kidney itself.

There has been much dispute as to the method by which caffeine causes diuresis. According to one view the primary and essential effect of caffeine is to increase the blood-flow through the kidney by provoking dilatation of the renal vessels with or without a rise in systemic blood-pressure. In many experiments the diuresis provoked by caffeine has been found to be closely associated with an increase in blood-flow through the kidney, but in other experiments this association has proved irregular or absent. Richards and his co-workers have shown that both the number of functionally active glomeruli and their degree of activity are widely variable under experimental conditions and are increased by caffeine. Caffeine may, therefore, increase the secretion of urine by increasing the functioning surface of the glomerular capillaries rather than by altering the permeability of the glomerular epithelium as originally postulated by Cushny.

In the caffeine diuresis the fluid part of the urine is increased chiefly, but the solids also undergo an augmentation, though not to the same

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extent. Among the solids the chief increase is seen in the sodium chloride, the nitrogenous constituents undergoing less alteration, although they also rise in amount. According to some observers, caffeine increases the chloride content of the blood and causes a loss of chloride and water from the tissues, the rise of blood chloride preceding the diuresis. It is possible therefore that the diuretic action of the caffeine group is at least partly due to an action on the tissues causing a transfer of their chloride to the plasma with an increase in its non-colloidal content which in turn causes the diuresis. The dilution of the urine reduces the concentration of acid, and in addition the alkali of the blood escapes through the kidney in larger quantity, so that the urine in caffeine diuresis is more nearly neutral than normally.

The excretion of large quantities of fluid in the urine is of course, accompanied by a diminution of the fluids of the blood, but the latter soon recuperates itself from the tissues. If there is any accumulation of liquid, such as edema, it is drained into the blood to replace the fluid thrown out by the kidney, and caffeine may accordingly be used to remove edema or dropsy in this way. If no such accumulation exists, the blood draws on the fluids of the intestine and stomach, and their withdrawal leads to the sensation of thirst. As a diuretic, caffeine is distinctly inferior to theobromine; in the first place, because the diuresis is less certain and is often accompanied by nervous symptoms—sleeplessness and restlessness; and secondly, because the increase in the secretion is smaller and lasts for a shorter time. Theophylline acts on the kidney even more powerfully than theobromine.

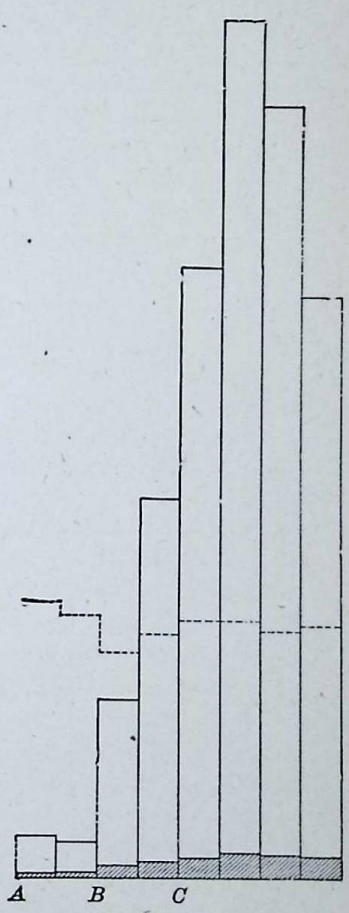

FIG. 30.—Caffeine diuresis in a rabbit. The amount of urine passed in ten minutes is represented by the height of the rectangles. The first of these, *A–B*, represent the normal secretion. At *B* a small dose, and at *C* a large dose of caffeine was injected intravenously, and the secretion is accordingly increased. The shaded part of the rectangles represents the amount of solids in the urine. It will be noted that these are increased but not in the same ratio as the fluid. The dotted line represents the average height of the blood-pressure during each period of ten minutes.

Excretion.—Caffeine undergoes decomposition readily in the tissues, and the whole is destroyed or excreted within twenty-four hours. During its passage through the body it loses its methyl groups and first becomes dimethyl- and then monomethylxanthine. Eventually xanthine is formed and this probably is converted into urea. In the urine are found small quantities of the unchanged

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drug, accompanied by larger quantities of dimethylxanthine and monomethylxanthine. After theobromine and theophylline some of the unchanged drug is found in the urine along with monomethylxanthine. The uric acid of the urine is not increased by any of these drugs.

Tolerance.—A certain degree of tolerance is acquired from the prolonged use of coffee, tea, or chocolate, as is shown by the absence of diuresis. Apparently the caffeine and its allies undergo more rapid destruction, but this does not explain the tolerance completely; the tissues also cease to react to their presence after prolonged use.

Preparations.—Because of their slight solubility in water, the xanthine derivatives are used in the form of their readily soluble double salts when injected. When given by mouth, either the free bases or the double salts may be used. Caffeine is used as the free base, as citrated caffeine (a soluble mixture of caffeine and citric acid) or as the double salt caffeine with sodium benzoate.

Theobromine is generally given in the form of a soluble double salt such as theobromine-sodium-salicylate (diuretin) or theobromine-sodium acetate—the former containing about 47 per cent of theobromine, while the latter contains about 63 per cent. *Theocalcin* is a double salt or mixture of calcium theobromine and calcium salicylate and contains 44 per cent of theobromine. It is less soluble than are the compounds mentioned above, and on that account is said to produce less gastric irritation.

Theobromine preparations are only given by mouth.

Theophylline (also known as theocin) is used as the free base, or in combination with ethylene diamine. The latter is also known as **aminophylline** and contains about 70 per cent of theophylline. Aminophylline is available in the form of tablets for oral administration, as a sterile solution for intramuscular or intravenous injection and in the form of rectal suppositories. When injected intravenously, infusion should be performed very slowly in order to avoid untoward effects. The double salt of theophylline and sodium acetate which is also known as **theocin soluble** is used orally.

Therapeutic Uses.—The action of caffeine on the central nervous system has led to its employment in a number of different conditions; thus, in *nervous exhaustion* it may be used to stimulate the brain, and in collapse its action on the respiratory center has been found of value. In *narcotic poisoning* with failing respiration, caffeine may be used to stimulate the center and is usually preferable to strychnine or atropine; in opium poisoning more particularly, strong coffee has long been used, but caffeine might be substituted with advantage. Its stimulant action on the brain, and more especially on the respiration, renders it an antidote in dangerous cases of alcoholic poisoning also. In such conditions it is most effective by hypodermic administration in doses of 0.5 to 1 gram of caffeine sodium benzoate. Some forms of *migraine* and headache are relieved by caffeine, but in others it seems rather to intensify the pain; this effect probably arises from the action on the brain and may be compared to the relief of fatigue; headache is often

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treated by a mixture of caffeine and one of the antipyretic series, such as phenacetine.

The principal therapeutic value of the xanthine drugs depends upon their action as diuretics although they are far less effective for this purpose than the mercurial compounds described on page 142. However, in patients with renal insufficiency in whom the mercury diuretics are contraindicated the xanthine drugs are depended upon. The modern use of diuretics in aiding in the elimination of edema has no doubt contributed greatly to the prolongation of life in patients with cardiac failure. Theophylline ethylene-diamine (aminophylline), theophylline sodium acetate (theocin soluble), theobromine and sodium acetate and theocalcin are the drugs used for this purpose.

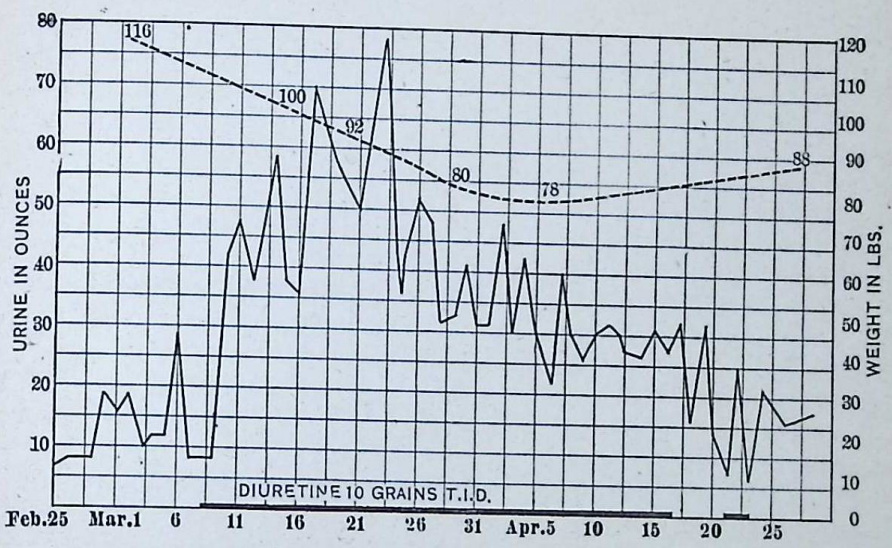

FIG. 31.—Action of theobromine in cardiac dropsy. A case of cardiac dropsy treated with diuretin (theobromine-sodium-salicylate) during the period marked with the black line below. Dose, 0.6 gram three times a day. The urine per day in ounces is marked in the unbroken line. The body weight fell continuously (dotted line) as the dropsy disappeared, and when the normal weight of almost 80 pounds was reached, the diuresis became less marked, as there was no longer so much fluid to draw upon.

Theophilline and theobromine preparations are widely used in angina pectoris to decrease the number and severity of attacks. In carefully controlled studies it has been found that placebos are equally effective insofar as the patients' subjective symptoms are concerned. For this reason the value of the xanthine drugs in coronary artery disease has been viewed with skepticism. However, Brown and Riseman have claimed that the ability to withstand physical exertion without pain is enhanced by the administration of the xanthines which conforms with the experimental evidence for their dilator effects. Whether the diseased coronary vessels react in a way similar to that in the normal is of course problematical.

The xanthine derivatives have proven to be of value in the treatment of severe attacks of asthma particularly of the so-called *status asthmaticus*. In patients refractory to epinephrine the slow intravenous injection of

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0.25 to 0.5 gram of theophylline with ethylene diamine (aminophylline) in 10 cc. of isotonic saline may give relief where other measures have failed. Whether this beneficient effect is due to relaxation of the bronchioles or to the dilating effect of the drug on the pulmonary vessels is not settled.

Coffee and Tea

Coffee is not used in medicine, but is of great dietetic importance The coffee bean contains about 1 to 2 per cent caffeine, and a cup of coffee is equivalent to 0.1 to 0.2 gram of caffeine along with some volatile substances, such as furfuralcohol, produced by the roasting; these have been called *Coffeon* and resemble in their action the volatile oils.

Tea contains a larger percentage of caffeine (about 1½ to 4 per cent), but as less tea is used than coffee, each cup may be considered to contain 0.1 to 0.2 gram. In green tea there is a considerable quantity of a volatile oil which also passes into the infusion, and the flavor of black tea also arises from volatile substances (*Theon*). Both black and green tea contain about 7 per cent of tannic acid, but this is only extracted slowly; however, the bitter taste in tea that has been prepared too long is due to the tannic acid.

The wakefulness and the relief from fatigue which are produced by tea and coffee are undoubtedly due to the caffeine contained in them. On the other hand, the feeling of well-being and comfort produced by coffee after a full meal is similar to the carminative effects of the volatile oils and appears to be due to the local action in the stomach of the volatile constituents of coffee. Apart from this local action, these volatile bodies seem to have no effect whatever on the economy. There is a widespread belief that excessive tea-drinking disturbs gastric digestion and this has generally been attributed to the tannic acid contained in it. It is not unlikely that the caffeine and theophylline may also play a part in this gastric action by causing irritation of the mucous membrane. Excessive consumption of tea or coffee may produce, in addition to digestive disturbances, increased nervous excitability, tremor, palpitation and insomnia, effects directly due to the caffeine content of these beverages.

Chocolate contains theobromine (0.5 to 1 per cent), instead of caffeine, and besides this a large amount of fat (cacao-butter, 15 to 50 per cent), starch and albumins. The theobromine does not possess the stimulant action of caffeine on the nervous system, and chocolate may therefore be taken where coffee or tea produces wakefulness. The starch and fat are assimilated by the tissues so that chocolate is a true food. Neumann found that cocoa retards the absorption of the proteins and fats of the food, especially those forms of cocoa in which the fat has been partially removed. On the other hand, cocoa with a large percentage of oil delays the gastric secretion and may give rise to a feeling of heaviness and discomfort in the stomach. Its continued use may cause dyspepsia, partly from this cause and partly from theobromine acting on the gastric mucous membrane. The food value of

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cocoa and chocolate (apart from that of added sugar) is often overestimated. It allays hunger, but this is only in part from its being a food, the local detrimental effect on the gastric mucous membrane tending to lessen appetite.

Minor Diuretics

A large number of vegetable drugs enjoyed a reputation in the past as diuretics but have been displaced by the effective xanthine and mercury diuretics, ammonium chloride and urea. The last named is non-toxic and may be given in large doses (1 to 5 grams, three or four times daily) to patients who do not have an elevation in non-protein nitrogen of the blood without undesirable reactions. Water itself is an excellent diuretic and many of the vegetable drugs formerly used owed their position merely to the large quantities of water in which they are taken; and some of them, such as barley, only lend body and taste to water. Others have a slight diuretic action in themselves but are superfluous since the introduction of more effective compounds.

Uva Ursi, the leaves of the bearberry, Arctostaphylos uva ursi, and of allied plants, contains two glucosides, *Arbutin* and *Methylarbutin*, along with large quantities of tannin and some inactive bodies. These glucosides are decomposed by the action of acids or of emulsin into glucose and hydroquinone or methylhydroquinone, and this change seems to occur in the body, for some hydroquinone appears in the urine though most of the arbutin is excreted unchanged. Uva ursi is found to have some diuretic action and the urine is found to undergo putrefaction more slowly than usual. Both these effects appear to be due to the undecomposed arbutin, though the hydroquinone may reinforce the glucoside in retarding putrefaction.

Buchu, the leaves of several species of Barosma, contains a volatile oil, which is excreted by the kidneys and increases the urine slightly; it also has a feeble antiseptic action in the urine.

Scoparius, the tops of the common broom plant (Cytisus scoparius), contains a resinous substance, scoparin, which seems to act on the kidney as a mild diuretic and accounts for the reputation which broom-tops once enjoyed.

Preparations

U. S. P.

Caffeina, as in B. P. Dose, 0.2 gram.

Caffeina Citrata, a white powder consisting of a mixture of about equal parts of citric acid and caffeine. It is soluble in 4 parts of water. On diluting this solution with an equal quantity of water, a portion of the caffeine gradually separates out but redissolves on further addition of water. Dose, 0.3 gram.

Caffeina et Sodii Benzoas, a mixture of equal parts of caffeine and sodium benzoate, dissolves in about its own weight of water. Dose by mouth or intramuscularly, 0.5 gram.

Injectio Caffeinæ et Sodii Benzoatis, an aqueous sterile solution. Dose, 0.5 gram intramuscularly.

Theobromina et Sodii Acetas, a hydrated mixture of theobromine sodium and sodium acetate in approximately molecular proportions. Dose, 0.5 gram.

Capsulæ Theobrominæ et Sodii Acetatis. Dose, 0.2 gram.

Theophyllina, or Theocine, is a white crystalline powder, soluble 1 to 120 in cold water, more soluble in hot water. Dose, 0.2 gram in powder or tablets.

Tabulæ Theophyllinæ. Dose, 0.2 gram.

Theophyllina Æthylenediaminica, white or slightly yellowish granules, containing approximately 75 per cent of theophylline, soluble 1 in 5 of water. Dose, 0.2 gram.

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THEOPHYLLINA ET SODII ACETAS, a white crystalline powder, containing about 60 per cent of theophylline, soluble 1 in 25 of water. Dose, 0.2 gram.

INJECTIO THEOPHYLLINE ÆTHYLENEDIAMINICÆ.

TABELLÆ THEOPHYLLINE ÆTHYLENEDIAMINICÆ.

B. P.

CAFFEINA, long, white, silky crystals, without odor, but possessing a bitter taste, soluble in 80 parts of cold water, more so in boiling water. Dose, 0.12 to 0.3 gram. Caffeine is best prescribed either in powder or in tablets. It may also be given in water with salicylate of sodium, which aids its solution.

CAFFEINA ET SODII BENZOAS, a mixture of equal parts of caffeine and sodium benzoate, a white, odorless, slightly bitter powder, completely soluble in 4 parts of water. Dose, 0.3 to 1 gram; by injection, 0.12 to 0.3 gram.

THEOBROMINA ET SODII SALICYLAS, a white, odorless powder, with sweetish taste; soluble in 1 part of water. Dose, 0.6 to 1.2 gram.

THEOPHYLLINA, theophylline, see under U. S. P.

THEOPHYLLINA CUM ÆTHYLENEDIAMINA, theophylline with ethylenediamine, aminophylline. Dose, 0.1 to 0.3 gram.

THEOPHYLLINA ET SODII ACETAS, a white, odorless powder with bitter taste; soluble in 25 parts of water. Dose, 0.12 to 0.3 gram.

MERSALYLUM, mersalyl, a white bitter deliquescent powder.

INJECTIO MERSALYLI, injection of mersalyl. Dose, 0.5 to 2 mil.

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C. LOCAL ANESTHETICS

I. COCAINE

Cocaine is an alkaloid obtained from the leaves of Erythroxylon coca and other species of Erythroxylon. The coca tree is indigenous to Peru, Bolivia, and adjoining areas of South America, where it has been in use for centuries. It has been introduced into India, Ceylon, and Java. The leaves of the coca grown in Peru and Bolivia contain cocaine along with small quantities of other alkaloids, but the Indian coca and still

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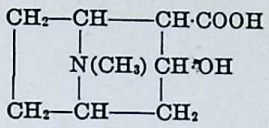
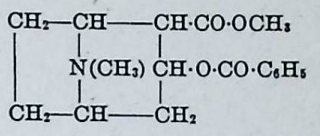
more the Java leaves contain a smaller proportion of cocaine and a larger amount of the less known alkaloids.

Cocaine is methylbenzoyl-ecgonine. On heating it with water, methyl alcohol is thrown off, leaving *Benzoyl-ecgonine*, which may be further broken up into benzoic acid and *Ecgonine*.

Ecgonine



Cocaine



Ecgonine is closely related to tropine (p. 463), a constituent part of atropine, differing from it in possessing a carboxyl group.

Many artificial cocaines have been formed by substituting other radicals for the methyl or benzoyl in this formula, and several of these have since been found in the cultivated plant, as for example, *Cinnamyl-cocaine*, in which cinnamyl occupies the position of benzoyl in the above formula. Various other alkaloids, such as *truxillyl-ecgonine*, and decomposition products are also present; all of these contain the ecgonine molecule in combination with various acids, and cocaine may be formed from all of them by isolating the ecgonine and combining it with benzoic acid and methyl. These alkaloids are present in the plant in very small quantities compared with cocaine. Another alkaloid which has been found in the Java coca is *Tropacocaine*, which is a combination of benzoic acid and a base $C_8H_{15}NO$.

The most important effects of cocaine are those on the central nervous system and on the sensory nerves.

Symptoms.—The symptoms of cocaine poisoning in man vary a good deal in different individuals. In most cases small quantities produce some excitement, pleasurable or disagreeable. The patient is generally restless and more garrulous than in ordinary life, often somewhat anxious and confused. But very often a small dose is followed by a calm, languorous state, somewhat resembling that induced by small quantities of morphine, but differing from it in there being less tendency to sleep. The pulse is accelerated, the respiration is quick and deep, the pupil generally dilated, and headache and dryness of the throat are complained of. The reflexes may be found somewhat more easily excited than usual and tremors or slight convulsive movements often occur; tonic or clonic convulsions sometimes supervene later, the heart becomes extremely accelerated, the breathing becomes rapid and dyspneic and may be finally arrested during a convulsion. In most cases the convulsive seizures are entirely absent, however, and fainting and collapse occur, apparently from the rapid absorption of a large dose. The skin is cyanotic and cold, the heart slow and weak; the respiration is very much depressed and death follows from its gradual cessation. Vomiting is occasionally seen at an early stage, but is not by any means common.

In the dog, cat and rabbit the symptoms are invariably those of stimulation of the central nervous system. Soon after the injection the animal shows symptoms of great restlessness and excitement; it seems unable to keep still, the dog at first showing all the signs of affection and excitement which he displays on ordinary occasions on

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being unchained or taken for a walk, but afterward running continually in a circle and paying but little heed to anything around it. Still later regular convulsions occur, and these are at first clonic, but may afterward become tonic, and then resemble those seen in strychnine poisoning. Even before the convulsions appear the animal seems partially unconscious, and in the intervals between them it lies in an apathetic state, which soon deepens to coma and death from asphyxia.

In the frog a certain amount of stimulation of the central nervous system is often displayed after small doses—increased movement, exaggerated reflexes and occasionally convulsions—but these soon pass into depression and eventually total paralysis of the central nervous system, while the peripheral nerves still maintain their function.

General Action.—Many of these symptoms point to a stimulant action on the **Central Nervous System**, resembling closely that seen in atropine poisoning. Thus the garrulity which is so often produced by cocaine, indicates augmented activity of the cerebrum, and the increased movement in the lower animals distinctly points to an affection of this part of the brain, for the movements are perfectly coördinated, and, in fact, in the early stages resemble exactly those performed by the normal animal in a condition of excitement. Further evidence of the action of cocaine on the cerebrum is offered by its effects on muscular work. The natives of Peru and Bolivia have used it for centuries to increase their endurance of fatigue. The bearers of the Andes, for example, march for hours with very little rest or food when they are supplied with coca leaves to chew. The effects of cocaine on the muscular power and on fatigue have been investigated also by means of the ergograph and dynamometer, and all observers agree that much more work can be done after cocaine than before it, and that it has a surprising potency in removing fatigue. As regards mental work, its effects are less known, but on the analogy of caffeine it may be supposed to increase the mental powers also when taken in small quantities. Some travellers in South America relate marvellous tales of its producing feelings of the highest bliss and power, but these have not been confirmed by experience of the action of cocaine in less romantic regions of the globe. Cocaine in small quantities, then, increases the higher functions of the cerebrum, while in somewhat larger doses the stimulant effect spreads to the lower areas and produces a very great increase in movement, accompanied, it would seem, by a depression of the consciousness. At the same time, the coördinating or balancing powers seem affected, so that the animal generally moves in a circle, the symptoms resembling the forced movements often seen in affections of the cerebellum.

The motor areas of the cerebrum have been found to be more easily stimulated by the electric shock when cocaine is injected, though when it is painted on the surface of the brain it lowers the irritability, owing to its being present in too great concentration. Still larger quantities induce convulsions, which are not of spinal origin, but point rather to action on some undetermined part of the hind brain. At an early stage the medulla oblongata is affected, as is shown by the quickened res-

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piration, and the exaggerated reflexes indicate stimulation of the spinal cord, which may be so great after very large doses as to cause convulsions like those produced by strychnine. The action of cocaine on the central nervous system is primarily a descending stimulation, the cerebrum being first affected, then the hind brain and medulla oblongata, and last of all the spinal cord. Perhaps it might be better expressed by saying that after small quantities the chief symptoms arise from the cerebrum, but as the dose is increased those from the lower parts of the central axis tend to become more prominent. After the stimulation there succeeds depression, which follows the stimulation downward, affecting first the cerebrum and then the lower divisions. The two stages are not definitely divided, however, one part of the cerebrum often showing distinct depression, while another is still in a condition of excessive activity. In some cases, especially in man, when a large dose is rapidly absorbed, the stage of excitement may be very short or apparently absent and the whole course of the symptoms then points to medullary depression.

The **Respiration** after cocaine is much accelerated, owing to central stimulation. At first the depth of the movement is not changed, but as the acceleration progresses the air inspired with each breath gradually becomes less. During the convulsions the respiration is irregular or ceases, but it recovers again in the intervals, until after a very violent paroxysm it fails to be reinstated. In other cases the breathing becomes slower and weaker after a time, and eventually stops from paralysis of the center. Periodic respiration is frequently seen, of the form generally known as Cheyne-Stokes.

The **Circulation** is altered by cocaine, owing to its action on the heart and on the vessels. The heart is much accelerated in mammals, while in the amphibians this is less often observed. The quickening has been ascribed to paralysis of the inhibitory terminations, but this seems not to be the case, for stimulation of the vagus slows the heart even late in the poisoning. The heart is accelerated, then, either by direct action on the muscle or by stimulation of the accelerator mechanism. It is often slow before death, but apparently not invariably, and this is probably due to direct action on the muscle. A large dose injected intravenously may cause rapid cardiac failure. In the frog's heart the inhibitory apparatus is paralyzed, the ganglia being affected in the same way as by curare and other drugs.

The vessels are much contracted in the earlier stages of poisoning, and this, together with the increased output of the heart, leads to a very considerable rise in the blood-pressure. The constriction of the vessels seems due to stimulation of the vaso-constrictor center, for it is absent after section of the spinal cord. When applied to mucous membranes, cocaine constricts the vessels from direct action on their walls, but there is no reason to believe that these are affected in general poisoning, since the necessary concentration would prove fatal from action on the heart and respiratory center.

Cocaine in low concentrations stimulates most forms of **smooth muscle**, *e. g.*, of the stomach, intestine and uterus, while higher concentrations relax or paralyze the muscle. Considerable variations have been found in different species of animals in the response of smooth muscle in particular organs. The dilatation of the pupil and constriction of the vessels suggested a stimulation of sympathetic nerve-ends, but a wider survey of the actions of cocaine provides no real parallel between its actions and sympathetic stimulation. However, cocaine has the property of potentiating the responses of organs innervated by the sympathetic

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to epinephrine as well as to sympathetic nerve stimulation. This potentiating effect has been explained by assuming that cocaine inhibits the destruction of epinephrine and hence prolongs its action.

The **Urine** is sometimes increased by cocaine, while in other instances its injection has been followed by total anuria lasting for several hours. This suggests that the action is not a direct one on the kidney, but is caused merely through the changes in the caliber of the vessels.

The other **Secretions** seem rather decreased than augmented, but no very marked effects are produced on them.

The **Temperature** generally rises in cases of poisoning, sometimes as much as 3° to 5° C. This pyrexia is presumably due to the combined effects of the drug (1) in augmenting heat production as a result of increased muscular activity, (2) in causing vasoconstriction which decreases heat elimination, and (3) in a direct action on the temperature regulating centers of the mid-brain. Cocaine pyrexia is usually preceded by a chill.

Some cocaine is **Excreted** by the kidney, the amount (from 1 to 16 per cent) varying in different animals. Part of this variation has been attributed to reabsorption from the bladder. The remainder of the drug is destroyed in the liver.

Tolerance appears to be attained in man when cocaine is used habitually, but this is not as striking as in morphine addiction. In animals repeated injection leads to a cumulation of cocaine in the tissues and hence the animal instead of becoming more tolerant becomes more susceptible to each new injection.

Cocaine Habit.—Since the introduction of cocaine into general therapeutic use, numerous cases of the formation of a habit similar to that of opium or morphine, have been recorded. This habituation differs, however, from the physiological dependence or addiction which occurs with opium and its derivatives.

Habitués usually take cocaine as a snuff, and this practice leads in many cases to ulceration or even perforation of the nasal septum. Some tolerance is produced to it but never so high as to morphine. As a rule, the practice is indulged in more intermittently than of morphine; and the abstinence symptoms are usually less serious than those following the withdrawal of morphine. The symptoms of cocainism generally begin with digestive disorders, loss of appetite, salivation and emaciation, but the more important changes occur in the central nervous system, which apparently undergoes degeneration similar to that seen in chronic morphine poisoning. Sleeplessness, tremors and occasionally convulsions, hallucinations, insanity, and delirium have been noted after long abuse, along with indefinite disturbances of sensation and motion. The cocaine habit seems to lead more rapidly to mental, moral, and physical deterioration than the morphine habit. The treatment of these cases is the withdrawal of the drug, and this can generally be done without the production of any special symptoms, though it is sometimes followed by great depression.

Local Action.—Cocaine applied locally in most parts of the body produces a loss of sensation through its paralyzing the **Terminations of the**

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Sensory Nerves, particularly those conveying impressions of pain and touch. At first heat and cold are recognized as readily as in the unaffected parts of the body. Cocaine applied to the tongue removes the taste of bitter substances, while sweet and acid fluids lose their taste only partially, and salt is recognized as easily as usual. A solution applied to the nasal mucous membrane paralyzes the sense of smell entirely.

The anesthesia or insensibility to pain and touch may be induced in any of the mucous membranes that can be reached by cocaine in sufficient concentration—pharynx, larynx, esophagus, stomach, nose, eye, urethra, bladder, vagina, and rectum. Applied to the unbroken skin its effects are less marked, as it penetrates but slowly through the horny epidermis; but when the epidermis is removed by abrasions or by skin disease, the cutaneous organs of sensation are acted on in the same way as those of the mucous membranes. The deeper sensory terminations can also be acted on by hypodermic injection, which causes a feeling of numbness and the relief of pain in the part. Hypodermic injection reaches not only the nerve terminations of the subcutaneous tissues, but also the finer nerve bundles, and these too are rendered insensible as far as the solution extends to them. The part may therefore be cut into or be subjected to other surgical treatment without pain, as long as the knife does not pass beyond the area to which the drug has penetrated, and numbers of grave surgical operations have been performed under the local anesthesia produced by cocaine.

Injected into the neighborhood of a nerve trunk, cocaine penetrates into the fibers and induces anesthesia of the organs supplied by the nerve, and injected into the spinal canal it causes anesthesia over large areas of the body, sometimes over almost the whole body, from its acting on the posterior roots of the cord. It must be noted that the anesthesia is only produced by the local application of the drug. The internal administration only leads to a partial loss of sensation in the throat and stomach, and no anesthesia is induced by its action after it reaches the blood-vessels. The reason for this evidently is that in order to paralyze the sensory fibers and terminations a considerable amount of the drug is required, but much less is necessary to paralyze the central nervous system. Even in the frog the sensory terminations are not fully paralyzed until all symptoms of reflex excitability have disappeared and total paralysis has supervened.

Cocaine applied to a nerve trunk proves to have a distinct selective action, for the sensory fibers fail to conduct sensory impressions, while motor impulses pass through the fibers without difficulty. Similarly, when it is injected into the spinal canal, complete loss of sensation in the lower part of the body follows, but the movements are almost unimpaired. This selection is only relative, for larger quantities paralyze the motor nerve fibers also. This difference in the reaction of the two sets of fibers is due to the difference in the size of the nerve fibers concerned with different functions. The afferent sensory fibers are small and hence are more readily penetrated and affected by a local anesthetic than the larger efferent motor fibers. Likewise, when cocaine is applied to the vagus nerve, it paralyzes the cardiac inhibitory fibers,

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which are small, while the larger afferent fibers which convey impulses to the respiratory center are more resistant.

When cocaine is applied locally to a mucous membrane it produces, besides a loss of sensation, a feeling of constriction and a distinct pallor and contraction of the vessels, due to a local action on the vessel walls.

The anesthesia produced by cocaine is comparatively short, but varies with the strength of the solution applied and with the vascularity of the part; as soon as the cocaine is absorbed, the local action disappears and sensation returns.

The prolonged muscular cramp seen in various nervous diseases and notably in tetanus, disappears when cocaine is injected into the muscles; this has been attributed to its paralyzing the sensory terminations in the muscle and thus arresting the proprioceptive stimuli which, passing to the spinal cord from the muscle, maintain its excessive activity. But if, as is asserted, cocaine also arrests the muscular contractions induced by nicotine, guanidine, etc., even after degeneration of the nerves, this explanation is insufficient and the action must be an antagonistic one on the receptors affected by these substances (Frank).

Cocaine applied to the **Eye** produces local anesthesia with contraction of the conjunctival vessels, followed by dilatation of the pupil and often by partial loss of the power of accommodation. The dilatation of the pupil is much less than that produced by atropine, and differs from it in several respects. Thus, the light-reflex is preserved, the pupil contracting in bright light and dilating further in the dark; a number of drugs which have little or no effect after atropine, contract the cocainized pupil (pilocarpine, muscarine, physostigmine), while atropine dilates it still further, and cocaine produces some dilatation after the full atropine action has been elicited. The motor oculi nerve is not involved in the action of cocaine, unless very large quantities are applied, when its terminations may be depressed in the same way as by atropine. It is believed that cocaine dilates the pupil by exerting a sympathicomimetic action on the dilator muscle (Fig. 35, page 468) in the same way as epinephrine. But this is not established by any satisfactory evidence, and cocaine differs from epinephrine in not affecting the sympathetic fibers in other organs.

The effect on the intra-ocular pressure seems to vary; it is sometimes reduced, from constriction of the vessels perhaps, while some cases are recorded in which the use of cocaine was followed by an acute attack of glaucoma, which is ascribed to the cocaine relaxing the iris and thus impairing the escape of fluid from the eye in the way which is more familiar under atropine.

Cocaine applied to the eye may cause clouding and ulceration of the cornea. This in addition to its mydriatic action have led to its replacement to a large extent in therapeutics by other local anesthetics.

General Protoplasmic Action.—The effects of cocaine on the nerve fibers and sensory terminations is so striking that its toxic action on other forms of living matter is liable to be forgotten. The anesthetic action is, however, merely an instance of its general toxicity, for if brought in contact with other forms of living matter in the concentra-

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tion used in anesthetizing nerve-ends, it is poisonous to all the structures which have been examined. Even concentrations too low to act on the peripheral nerves act on the nerve cells and paralyze them, so that it is impossible to induce a general loss of sensation by cocaine injected into the circulation, and local anesthesia can be induced only by applying relatively strong concentrations and confining their action to definite areas. The ciliated epithelial cells, leucocytes and spermatozoa become motionless, the cortical nerve cells lose their excitability, and many of the invertebrates are killed by even a short exposure to cocaine. The movements of protoplasm in plants are also retarded or entirely suppressed by this poison, and the process of putrefaction is delayed considerably. In some cases, notably in the higher invertebrates, the final depression is preceded by a stage of increased movements, and vertebrate muscle cells, whether striated or unstriated, are first aroused to greater activity and then depressed and paralyzed. In some other instances, however, cocaine induces only depression and paralysis.

Other examples of this destructive action are also seen in the clouding of the cornea which may follow the application of cocaine to the eye and the necrosis which sometimes follows its subcutaneous injection. Victims of the cocaine habit often show numerous scars on the arms and legs from this local gangrene, although this is probably often due to unsterilized syringes rather than to the solution.

Acute Cocaine Poisoning.—The symptoms of acute cocaine poisoning vary very much, depending upon the toxic dose and the rapidity of its absorption. In most cases convulsive symptoms are most prominent and should be controlled by the intravenous administration of a slow acting barbiturate. When a large dose has been rapidly absorbed, the symptoms may be mainly depressant, and artificial respiration may be necessary. Of course, the stomach ought to be evacuated first of all if the drug has been taken by the mouth and a tourniquet applied if the drug has been injected. Perhaps the bladder also ought to be evacuated to prevent the possibility of reabsorption of cocaine from that viscus. In cases where cocaine is to be used in surgery as a local anesthetic the previous administration of barbital or of one of the other barbiturates has seemed to lessen to a very considerable degree the likelihood of poisoning.

II. LOCAL ANESTHETICS

In the early days of local anesthesia with cocaine, a number of fatalities occurred from its use. These became less frequent with increasing experience of the margin of safety within which it could be used. However, the fact that it is a highly toxic substance and has also the serious drawback of habit-formation prompted the search for less dangerous substitutes. If adequate substitutes could be found, which do not give rise to habit-formation, there would be no excuse for the manufacture of cocaine and the illicit use of cocaine could be eliminated at its source. The local anesthetics are used for a great variety of purposes, and it is not necessary that cocaine should be completely replaceable by one substitute. It would be sufficient if for each different use of cocaine some less dangerous and equally efficient substitute could be found.

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In the search for substances to replace cocaine, over one hundred local anesthetics have been introduced, but only a few have been widely used, and of these only the most important can be considered here.

In addition to cocaine and its substitutes, other protoplasmic poisons such as quinine (in combination with urea) are occasionally used for local anesthesia. Freezing is also a procedure for abolishing pain and is sometimes used in surgery. Anesthesia can be induced in this way, for example, by packing an extremity in ice or by the application of volatile agents such as ethyl chloride (page 291.)

The ideal local anesthetic should have a wide margin of safety between the amount of the drug necessary to produce anesthesia and the toxic dose. The therapeutic index of the available synthetic local anesthetics is very variable. The drug must be soluble to permit its injection and rapid diffusion into the nerve fibers. In order to prevent their rapid absorption epinephrine is added to many of the local anesthetics in order to constrict the blood-vessels and thus delay the absorption of the anesthetic and prolong its action locally. An ideal local anesthetic should require little time for the onset of its action; should last for a long enough period to allow the desired surgical procedure to be performed; and should then leave no residual damage or effects on the nerves and tissues.

Chemistry.—The synthetic local anesthetics are tertiary amino esters of aromatic acids. Simple esters of amino-benzoic acid manifest some local anesthetic action but this is increased as the side chain is increased in length and when a tertiary amino group is introduced into the molecule.

In the accompanying table are listed some of the synthetic local anesthetics and their formulæ, which are included in the U. S. Pharmacopeia as well as several selected from the large group included in New and Non-official Remedies. Since the free bases are insoluble, they are used in the form of acid salts which are converted in the tissues to the free base which is responsible for the anesthetic effect.

Procaine which was introduced in 1905 under the trade-name "novocaine" is probably the most important of the local anesthetics and when injected it acts promptly and is non-irritant. It is the diethylamino-ethyl ester of para-aminobenzoic acid and is only about a fourth as toxic as cocaine. Its action is usually prolonged by the addition of epinephrine to the solution. It does not penetrate well when applied to mucous membranes so that it is usually given by hypodermic injection. It is prompt and powerful in its anesthetic action. The hydrochloride of procaine is the salt usually employed although the nitrate and borate are also used. The molecule of the last named salt is heavier than that of the hydrochloride and as it contains only 51.8 per cent of the base it has to be given in larger doses than the hydrochloride.

Procaine is destroyed mainly by the liver; although the other tissues possess some detoxifying action they act less promptly and less efficiently. Injected into the normal dog it disappears quickly from the blood,

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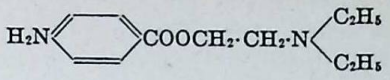
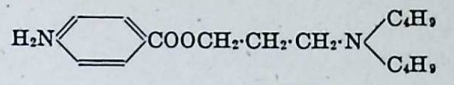
being converted into non-toxic end-products which are eliminated by the kidneys.

SOME SYNTHETIC LOCAL ANESTHETICS

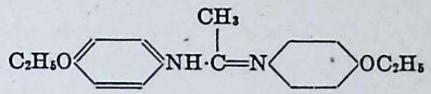
Procaine (Novocaine)



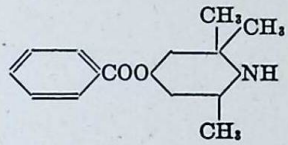
Butacaine (Butyn)



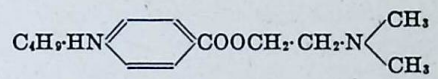
Phenacaine (Holocaine)



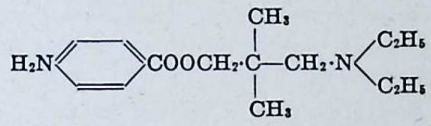
Eucaine (Betaeucaine)



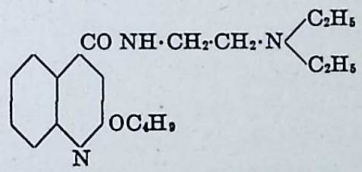
Tetracaine (Pontocaine)



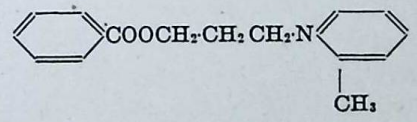
Larocaine N. N. R.



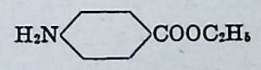
Nupercaine N. N. R.



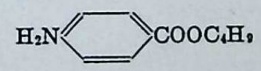
Metycaine N. N. R.



Ethylaminobenzoate (Benzocaine)



Butyl aminobenzoate (Butesin)



When used for infiltration anesthesia, 0.25 gram of procaine hydrochloride is dissolved in 50 or 100 cc. of isotonic sodium chloride and 0.3 or 0.6 cc. of a 1:1000 epinephrine solution added. For instillations and injections, 5 or 10 cc. of a 1 or 2 per cent solution with or without epinephrine (0.6 cc. of a 1:1000 solution) are used. When used in the eye, solutions varying in concentration from 1 to 10 per cent are employed; in the nose and throat, 5 to 20 per cent solutions are recommended

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with the addition of 0.5 cc. of a 1:1000 epinephrine solution to each 10 cc. of the anesthetic solution.

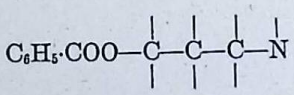
Butacaine (butyn) was introduced as a substitute for cocaine for surface anesthesia, particularly for use in the eye, nose and throat. It is the dibutylaminopropyl ester of para-aminobenzoic acid. It is more powerful than cocaine so that a smaller quantity is required, and its action is prompt and well sustained. It does not produce drying of the tissues nor does it dilate the pupil nor contract the blood-vessels.

When injected hypodermically into animals butacaine is several times as toxic as cocaine. It is thus unsuitable for injection or for spinal anesthesia. It is used principally in ophthalmological practice in the form of a 2 per cent solution. A single application produces, within one minute, anesthesia sufficient for minor manipulations while repeated instillations permit operation on the eye.

Phenacaine, originally designated by the trade-name *holocaine*, is a derivative of phenetidin. It is more toxic than cocaine on subcutaneous injection and hence its use is limited to topical applications, particularly for instillation into the eye. It exerts a quicker action than cocaine, 0.3 cc. of a 1 per cent solution being sufficient to induce anesthesia in one to ten minutes.

Eucaine (betaeucaine, benzamine), trimethyl-benzoyl-hydroxy-piperidine, was the first important synthetic substitute for cocaine.

Cocaine and eucaine resemble one another structurally in that both possess the grouping



Tetracaine (pontocaine) differs from procaine in that one of the amino hydrogens of the aminobenzoate group is replaced by a buytl group and the two ethyl groups of procaine are replaced by two methyl groups.

Pontocaine resembles procaine in its action but is more efficient when applied to mucous membranes so that it can be used in the eye, nose or throat. For the eye a 0.5 per cent solution is used and a 2 per cent in the nose or throat. Ten to 20 mg. in a 1 per cent solution is used for spinal anesthesia. For continuous caudal anesthesia 30 cc. of a 0.25 per cent solution is used initially with supplementary injections of 10 to 20 cc. at intervals of forty to ninety minutes as required.

Larocaine hydrochloride differs in structure from procaine in that it has a propanol group in place of the ethanol group with two methyl groups attached thereto. It is an efficient anesthetic whether applied locally to the mucous membranes or injected. The anesthesia is produced rapidly and is well sustained. A 2 to 5 per cent solution is used in the eye and a 5 to 10 per cent solution in the nose or throat. In urology, a 0.75 to 1 per cent solution is preferred.

Larocaine is also used for conduction anesthesia in a 0.25 to 2 per cent solution with the addition of epinephrine, when desired, just prior to administration.

Nupercaine (dibucaine), introduced as percaine, is 2-butyloxyquinolinecarboxylic acid-4-diethylethylenediamide. It acts like cocaine when

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applied to mucous surfaces and like either cocaine or procaine when injected. It is much more toxic than cocaine when injected intravenously into animals and is more active as an anesthetic than either cocaine or procaine when given subcutaneously. For infiltration anesthesia not more than 100 cc. of a 1:2000 to 1:1000 solution with the addition of 0.1 cc. of 1:1000 epinephrine per 100 cc. of solution, should be used. For spinal anesthesia, 7.5 to 10 mg. in 0.5 per cent solution and for sacral anesthesia, 25 to 35 cc. of a 0.1 per cent solution are used.

Metycaine [(2-methylpiperindino)-propylbenzoate] produces local anesthesia whether applied by injection or locally to mucous membranes. Its toxicity when it is injected subcutaneously is comparable to that of procaine; intravenously, it is about three times as toxic as procaine. It is more potent than procaine and is also a good surface anesthetic. A 1 per cent solution is said to act more quickly than a 1 per cent solution of procaine, and the anesthesia is more profound and more prolonged. For use in the eye a 2 per cent solution is used, while a 2 to 10 per cent solution is used in the throat or nose. For infiltration, in small areas, a 0.5 to 1 per cent solution is used. For spinal anesthesia 2 cc. of a 10 per cent solution of metycaine hydrochloride is used.

Ethyl aminobenzoate (*benzocaine, anesthesin*) and **butyl aminobenzoate** (*butesin*) belong to a group of local anesthetics which because of their slight solubility are unsuitable for injection. Their slow absorption, on the other hand, renders them less toxic and hence suitable for application to ulcers, wounds and mucous surfaces. They induce less complete anesthesia than the soluble local anesthetics but it is more lasting. Butyl and ethyl aminobenzoate are used principally as dusting powders. The combination of picric acid with butyl aminobenzoate (butesin picrate) is also used for the treatment of burns, ulcers and other painful lesions of the skin.

Among other local anesthetics included in New and Non-Official Remedies mention may be made of **alupin hydrochloride** (amydricaine), **amylsine hydrochloride** (amylcaine), **apothesine hydrochloride, benzylalcohol, diothane hydrochloride,** and **tutocaine hydrochloride** (butamin).

Differing in chemical composition from any of the foregoing, quinine and many of the derivatives have been found to possess a local anesthetic action, and of these **Quinine-urea** has been chiefly used for this purpose.

In comparing the **advantages** and drawbacks of the various local anesthetics, the chief points to be considered are, the general toxicity on absorption, the power of producing local anesthesia, the extent to which the paralysis of the nerve-ends is attended by irritation or injury of other cells in the neighborhood, and the local action on the vessels. The solubility of the substance is naturally also of importance, as is the power of penetrating the tissues.

The **toxicity** of a local anesthetic varies with the animal used and with the method and rate of injection, and therefore, in a comparison of the toxicity of different anesthetics, those factors have to be taken into account. For example, cocaine is more than five times as toxic as procaine by subcutaneous injection but less than four times by intra-

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venous injection. This difference is partly due to the fact that procaine is destroyed by the liver, whereas cocaine is not. When given by subcutaneous injection, owing to slower absorption, time is given for destruction of procaine by the liver with a consequent diminution in its toxicity. In whatever way it is administered procaine is less poisonous than cocaine, but if procaine be injected into the tissues and accidentally gains entrance into a vein, then its toxicity approximates more nearly to that of cocaine. For these reasons it is possible to give only an approximate comparison of the relative toxicities of the local anesthetics. The toxic symptoms produced by them very closely resemble those produced by cocaine, but none of them have so far proved to give rise to habit formation. Some, however, have an irritant and devitalizing action on the tissues. Procaine is especially free from this. Cocaine alone causes a shrinkage of the tissues due to contraction of the vessels; butyn causes actual hyperemia.

None of them penetrate mucous membranes so readily as cocaine, although some are quite efficient when used in this manner. The effect of butacaine so applied is less lasting than that of cocaine and is often followed by pain. Nupercaine seems to penetrate mucous membranes well and its effect is prolonged. Procaine produces at best delayed and incomplete anesthesia when applied to mucous membranes and is seldom used for surface anesthesia. Most of them can be sterilized by boiling, except cocaine, which is destroyed by prolonged boiling.

The action of the local anesthetics is quantitatively modified to an important degree by *simultaneous use of epinephrine*. By locally contracting the vessels, epinephrine produces the following effects. It relieves local congestion and lessens hemorrhage, effects which are sometimes desirable. The contraction of the vessels also delays the absorption of the local anesthetic. This allows longer time for excretion of the drug or for its destruction in the body and so diminishes its toxicity. By maintaining the concentration of the anesthetic at the point of application this not only prolongs the local anesthesia but renders this possible with a smaller quantity of the anesthetic. It must be remembered, however, that epinephrine, especially if it should gain entrance into a vein, is a very powerful poison, and it must be used with caution.

Therapeutic Uses of the Local Anesthetics

The therapeutic uses of cocaine and its allies are dependent on their anesthetic action. Because of its potential toxicity and tendency to addiction cocaine has been almost entirely superseded in therapeutics by other local anesthetics. One of the advantages of the substitutes for cocaine is that none of them seem liable to produce habit-formation. Only the general principles of local anesthesia can be discussed here. It will be convenient to discuss the various ways in which local anesthetics are employed and to indicate which of them have been found most suitable for each purpose. The intravenous injection of procaine has also been advocated for serum sickness, intractable pruritus, acute cardiac arrythmias occurring during anesthesia, etc.

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Surface Anesthesia.—When applied to a surface, local anesthetics can produce loss of sensation by their paralyzing action on afferent nerve-ends, provided that they can get access to these. They have little power to penetrate the *unbroken skin;* a 10 per cent ointment of cocaine produces only a slight dulling of sensation of the skin but no complete local anesthesia. For *wounds* and *ulcers,* where there is no horny epithelium to oppose penetration, insoluble local anesthetics have occasionally been used, but they are liable to produce severe irritation, and even sloughing, and they must be used with the greatest care if at all. Soluble anesthetics are too easily absorbed and their action is too transient for this kind of use.

Many of the local anesthetics penetrate *mucous membranes* readily, others do not.

Cocaine is unrivalled in its power of penetrating the mucous membranes; the hydrochloride is dissolved in 0.8 per cent sodium chloride solution, or better in Ringer's solution, in order to avoid the effects of water on the tissues. In ophthalmic surgery it was used very largely both during operation and to alleviate pain, and occasionally to constrict the vessels of the iris in inflammatory conditions, but it has been replaced in large part by superior substitutes such as butacaine. The anesthesia induced by cocaine is of short duration, generally setting in after five to seven minutes and passing off twenty to thirty minutes after the application of the drug. Occasionally cocaine, especially in strong solution, produces a certain amount of opacity of the cornea, and wounds heal less readily and irritant antiseptics are more dangerous with cocaine than without it. This arises from the general toxic action of cocaine on living matter, which tends to lessen the resistance of the tissues with which it comes in contact. The usual explanation given that cocaine paralyzes sensation in the cornea, and thus prevents the reflex winking which removes foreign bodies from the surface and keeps the eye moist, is obviously insufficient, as the anesthesia is of but short duration. The dilatation of the pupil produced by cocaine is much less complete than that under atropine and can only be taken advantage of in diagnosis by using a very dim light, as the pupil contracts in bright light almost to its normal size. On the other hand, cocaine is less injurious in glaucoma and the dilatation can be removed at once by the instillation of a few drops of physostigmine. Butacaine sulfate is a satisfactory substitute for cocaine in ophthalmologic practice and is superior to cocaine in several respects. It produces no drying of the tissues, no change in the size of the pupil, no ischemia and acts more rapidly and for a longer time with less danger of toxicity. It and other derivatives have displaced cocaine in ophthalmology.

In the nose, throat and larynx, cocaine was formerly used in a solution of 4 per cent, either painted or sprayed on the surface or soaked in gauze with which the nose is packed; anesthesia is obtained with greater difficulty than in the eye, and a considerable number of fatalities occurred from its use in nose and throat work. Cocaine has been superseded by one of the substitutes applied locally or given by submucous injection. For the nose or larynx cocaine should not be used in a concentration

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above 10 per cent or in a total quantity above 0.1 gram. Eucaine has also been painted or sprayed in 5 to 10 per cent solution but is less efficacious than cocaine. More recently nupercaine (percaine) has been used for producing surface anesthesia, and many authorities regard it as an efficient substitute for cocaine for this purpose. In the *urethra, rectum* and *vagina,* many cases of poisoning have arisen from urethral injection of cocaine (1 to 2 per cent) used either as an anesthetic or to relieve pain temporarily where trauma or stricture existed, so that it has been superseded for these purposes by less toxic local anesthetics such as alypin, butacaine, metycaine, etc.

Terminal Anesthesia.—When cocaine is injected under the skin or under a mucous membrane, it produces local anesthesia by paralyzing the afferent nerve-ends or the terminal nerve fibrils. In this case absorption may be rapid and full opportunity is given for the drug to exert its general toxicity. Cocaine was originally used especially in combination with epinephrine for this purpose, but it has been replaced by procaine and allied drugs. Procaine does not penetrate sufficiently well to be useful for surface anesthesia, but this lack of penetrating power does not affect its action when injected. When given with epinephrine its anesthetic action is sufficiently prolonged for most purposes and its toxicity is markedly reduced. For this form of anesthesia it is one of the safest and best of the local anesthetics.

The local anesthesia produced by cocaine or procaine, even when epinephrine is added, does not last much over an hour at most. This is sufficient for many purposes but not for relieving pain after many operations. Especially in operations for hemorrhoids quinine-urea has been widely used, in concentrations of 0.5 to 1 per cent. This solution causes irritation and transient pain on injection, followed by local anesthesia which may last for many hours or even several days. Quinine has little selective action on sensory nerves and the concentrations required to produce anesthesia have an injurious action on the tissues and may even produce necrosis. Quinine-urea has therefore to be used with care.

For many years after its introduction as a local anesthetic in 1884, the use of cocaine was practically limited to minor operations in the nose and throat and to ophthalmic surgery, few general surgeons venturing on its application except in quite minor operations which required only a small incision and no manipulation; for this purpose cocaine was injected into the site of operation, but its place has been taken by less poisonous members of the group, which are equally efficacious when injected under the skin and are less likely to cause general poisoning. Within recent years, however, the use of local anesthesia has undergone a wide extension, so that almost all the major surgical operations have been performed under it, and it has now become a major branch of anesthesia. Occasionally partial local anesthesia is combined with the administration of small quantities of the volatile anesthetics or one of the barbiturates which are insufficient to produce complete unconsciousness, but cause a numbing of the sensation, which, together with the local action, permits of a painless operation. Premedication with

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morphine or with some of the synthetic hypnotics or analgesics intensifies the local anesthetic action. At first, strong solutions were injected to prepare the way for the knife, each step forward in the operation being preceded by an injection to induce anesthesia of the layer of tissue to be incised. But this method, which was advocated by Reclus, is now scarcely used except for minor operations in which a single injection is sufficient.

A more satisfactory method of local anesthesia for operative purposes was introduced by Schleich under the name of **infiltration anesthesia.** A large quantity, generally about 100 cc. of a solution containing 0.1 per cent of procaine, 0.001 per cent of epinephrine, and 0.8 per cent of sodium chloride is allowed to permeate the tissues through a fine hypodermic needle. Only very slight pressure is required and the whole of the surrounding structures become swollen and edematous and can be cut into without pain. Much of the fluid escapes through the incision and no symptoms of poisoning arise.

Regional anesthesia consists in injecting a local anesthetic, *e. g.*, procaine in 2 per cent solution, into the immediate neighborhood of the nerve supplying the part to be operated on. Complete local anesthesia is obtained, and shock is less liable to occur than when general anesthesia is induced. This method has been used extensively in operations on the foot and hand, for which it is admirably suited; it can also be adapted to other parts of the body. The local action in both infiltration and regional anesthesia may be augmented and the danger of general poisoning lessened by retarding the circulation in the part to be operated on. This may be done by applying an Esmarch bandage above it when a limb is involved, but the best results are obtained by using a solution of epinephrine along with the anesthetic.

Another method of inducing anesthesia in a limb is by means of *venous* injection. The limb is emptied of blood by elevation and bandaging and a tourniquet is applied above the point where the injection is to be made; the anesthetic is now injected under some pressure into a superficial vein peripheral to the tourniquet and quickly penetrates by diffusion throughout the veins of the limb, paralyzing sensation wherever it reaches. After the operation the tourniquet is slowly loosened and the anesthesia disappears with the anemia. The same strength of solution is used as for infiltration anesthesia, and the quantity is too small to have any effect when it reaches the general tissues. Intra-arterial injection has also been employed in the same way in bloodless limbs. These procedures are rarely used today.

Spinal Anesthesia.—After it was found that the nerve impulses from the periphery to the central nervous system could be blocked by the injection of cocaine into the peripheral nerves, the next step was to obstruct them higher in their course by applying it to the spinal roots (*subarachnoid* or *intraspinal anesthesia*). The first to attempt this was Corning of New York, but the development of the procedure is due to Bier and Tuffier. A long, hollow needle was passed into the spinal canal between the laminæ of the lumbar vertebræ and 1 cc. of a 2 per cent solution of cocaine hydrochloride was injected after the withdrawal of

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an equivalent amount of cerebrospinal fluid. The actual amount of cocaine injected was thus 0.02 gram. Under cocaine, accidents were so numerous that the method was abandoned by conservative surgeons until it received a new lease when procaine was substituted for cocaine. Its use today is very common. Within a few minutes numbness begins, generally in the feet at first, but sometimes in the lower part of the trunk; it spreads upward rapidly until sensibility to pain is lost everywhere below the diaphragm and sometimes in the thorax; in some cases even the head has been found anesthetized. The sensations induced by warmth and cold are less quickly affected, touch is preserved to some extent and the limbs can be moved readily, though the movements are carried out more slowly than usual; the consciousness is unimpaired. This condition lasts from one-half hour to one hour and then sensation returns gradually. In the beginning of the action some muscular twitching is often seen, and the muscles are never as relaxed as they are under chloroform or ether. Vomiting occurs in a certain proportion of cases either during or after the operation, and persistent headache is often present. A more dangerous effect is the onset of collapse with very low blood-pressure and all the symptoms of cerebral anemia. This not infrequently fatal accident is attributed to the anesthetic paralyzing the vasomotor roots of the splanchnic nerves within the spinal canal (Smith and Porter). The anesthesia from the intraspinal injection arises from action on the posterior nerve roots and not on the cord itself. The cerebrospinal fluid has been found to contain a large number of polynuclear leucocytes after the injection and resumes its normal limpid character only after several days. This method of anesthesia has been used in a large number of operations, some of them of the gravest nature. For spinal anesthesia, procaine, tetracaine, nupercaine, etc., are most widely used.

Of these methods, Schleich's infiltration has been most widely adopted and is admirably suited for minor operations. It is the safest method available for most of these, for the amount of anesthetic injected is not sufficient to induce poisonous symptoms, and much of this escapes by the incision. It requires some experience to induce complete insensibility to pain by this method and the operation has to be interrupted at intervals to permit of further injections. Some headache and nausea are occasional sequelæ. When general anesthesia is contraindicated, infiltration may be adopted in major operations, while on the other hand it is often contraindicated in minor operations where there is any possibility of complications, or where the anxiety and nervousness of the patient are likely to interfere with the proceedings. Perhaps to a greater extent than with other methods of anesthesia, the safety and efficiency of spinal anesthesia depends upon the skill and experience of the anesthetist. It is usually recommended when special circumstances contraindicate the general anesthetics, and operation is imperative. Persistent and severe headaches occur occasionally after spinal anesthesia, and nausea is not uncommon. Fall of blood-pressure is frequent, for which some advocate ephedrine or epinephrine. More rarely serious

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circulatory or respiratory failure occurs during spinal anesthesia, in some cases at least apparently due to idiosyncrasy.

Caudal Anesthesia.—This form of anesthesia has been popularized during recent years particularly in obstetric practice. Caudal anesthesia is a form of regional anesthesia induced by injecting a local anesthetic into the epidural space through a needle inserted into the caudal canal. It should not be confused with spinal anesthesia in which the injection is made into the subarachnoid space. Repeated intermittent administration of small doses of the anesthetic allows a painless parturition without interfering with the consciousness of the patient or normal contractions of the uterus.

Although introduced originally by Hingson and Edwards for use in obstetrics, continuous caudal anesthesia has also been employed for operations involving the pelvis, perineum, and genital organs. Care must be taken to insure that the needle is inserted into the caudal canal and not in the subarachnoid space. A continuous drip of procaine, tetracaine, etc., is preferred to their intermittent injection.

Caudal or epidural anesthesia has the advantage over spinal anesthesia in that the anesthetic does not have direct access to the spinal cord and medullary centers. It, therefore, does not affect the motor nerves of the respiratory muscles or the blood-pressure and is less likely to cause undesirable symptoms. The application of epidural anesthesia requires experience, skill, and constant attention.

Physical Methods.—Various physical methods are also used to obtain local anesthesia. The use of a spray of ethyl chloride has already been referred to on page 291. Refrigeration of an extremity with the application of a tourniquet is used especially for amputations. In this procedure ice bags are applied for about twenty minutes to reduce sensitivity of the limb (arm or thigh). A tourniquet sufficient to shut off the blood and lymph supply is then applied about 6 inches above the site of the proposed incision. The limb is then completely surrounded by ice and covered with a rubber sheet. Anesthesia occurs in about two and one-half hours and lasts for about one hour. The ice is then removed and the amputation performed. Following surgery, ice bags are applied to the stump for forty-eight hours, a procedure which prevents postoperative pain and edema. Advantages claimed for this type of anesthesia are prevention of embolus and thrombus formation, decreased infection, lack of postoperative edema and pain in the stump. Preoperative medication is generally not necessary but is of value in lessening the apprehension of the patient in the operating room.

Preparations

U. S. P.

Cocaina, an alkaloid ($C_{17}H_{21}O_4N$) obtained from the leaves of Erythroxylon coca and other species of Erythroxylon, forming colorless crystals with a bitter taste followed by numbness; almost insoluble in water, soluble in alcohol.

Cocainæ Hydrochloridum ($C_{17}H_{21}O_4NHCl$), colorless crystals very soluble in water and alcohol; prolonged boiling of watery solutions causes the alkaloid to decompose.

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BUTACAINÆ SULFAS, butacaine sulfate, a white powder, soluble in water.

BUTYLIS AMINOBENZOAS (Butesin), a slightly soluble compound used as a dusting powder.

ÆTHYLIS AMINOBENZOAS (Benzocaine, Anæsthesine), used as a dusting powder.

UNGUENTUM ÆTHYLIS AMINOBENZOATIS, a 5 per cent ointment.

EUCAINÆ HYDROCHLORIDUM, colorless crystals, soluble 1 in 30 of water.

PHENACAINÆ HYDROCHLORIDUM (Holocaine), small colorless crystals, soluble 1 in 50 of water, freely soluble in alcohol.

PROCAINÆ HYDROCHLORIDUM (Novocaine), colorless crystals, freely soluble in water.

TETRACAINE HYDROCHLORIDUM (Pontocaine), a white powder, very soluble in water.

QUININÆ ET UREÆ HYDROCHLORIDUM, colorless crystals freely soluble in water.

B. P.

COCAINA, methyl benzoylecgonine, an alkaloid obtained from the leaves of Erythroxylum coca and other species of Erythroxylum, or by synthesis from ecgonine. Dose, 0.008 to 0.016 gram.

COCAINÆ HYDROCHLORIDUM. Dose as of Cocaina.

LAMELLA COCAINÆ, each contains 1.3 mg. of the hydrochloride.

OCULENTUM COCAINÆ, 0.25 per cent.

TROCHISCUS KRAMERIÆ ET COCAINÆ (3 mg. of the hydrochloride in each lozenge).

AMETHOCAINÆ HYDROCHLORIDUM, amethocaine hydrochloride, tetracaine hydrochloride, a white, crystalline powder, very soluble in water.

AMYLOCAINÆ HYDROCHLORIDUM (Stovaine), colorless crystals, freely soluble in water. Doses, by mouth and by subcutaneous injection, 0.02 to 0.05 gram; by intrathecal injection, 0.02 to 0.1 gram.

BENZOCAINA, Anæsthesine, a white crystalline powder, soluble 1 in 2,500 of water. Dose, 0.3 to 0.6 gram.

ORTHOCAINA, Orthoform-new, a white crystalline powder, sparingly soluble in water. Dose, 0.1 to 0.2 gram.

PROCAINÆ HYDROCHLORIDUM (Novocaine). Dose, 0.03 to 0.12 gram. By subcutaneous injection up to 1 gram, by intrathecal injection up to 0.15 gram.

INJECTIO PROCAINÆ ET ADRENALINÆ MITIS (B. P.), weak injection of procaine and adrenaline. This is prepared prior to use by mixing a sterile 2 per cent solution of procaine hydrochloride with three times its volume of physiological saline and 2 mil. of adrenaline hydrochloride solution for each 1,000 mil. of the final solution.

INJECTIO PROCAINÆ ET ADRENALINÆ FORTIS (B. P.), strong injection of procaine and adrenaline, contains procaine hydrochloride, 2 gram; sodium chloride, 0.5 gram; chlorocresol, 0.1 gram; solution of adrenaline hydrochloride, 2 mil.; sodium metabisulphite, 0.1 gram and freshly prepared distilled water sufficient to produce 100 mil.

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D. CURARE GROUP

I. CURARE

Curare (curara, woorara, urari or woorali) is an arrow poison used by the natives of South America, who prepare it by extracting the bark of plants of the genus Strychnos, such as *S. toxifera*. It is obtained mostly from the upper regions of the Amazon and the eastern slopes of the Ecuadorian plateau. The natives prepare an infusion which they concentrate to a syrup and package in gourds (*calabash curare*), bamboo tubes (*tubocurare*), or clay pots (*pot curare*). The most important active principle present in curare has the formula $C_{38}H_{44}O_6N_2$ and has been designated as *d*-tubocurarine (King). There is also present in the extract a related substance, curine ($C_{36}H_{38}O_6N_2$) which has only a weak curariform action on the nervous system but exerts other actions on the heart, blood-vessels and central nervous system. Other related compounds present in crude curare are curarine, protocurarine, protocurine and protocuridine. Of these only protocurarine ($C_{19}H_{23}O_2N$) has a strong curare-like action (Boehm).

Action.—The chief effect of curare is the arrest of all voluntary movements through an interruption of the connections between the peripheral nerves and the striated muscle fibers. In the mammal, the muscles give way one after the other until the animal lies helpless on the ground. It can still move its limbs, but cannot recover its ordinary position, and soon the limbs become totally paralyzed and the respiratory movements alone persist, although they too are slow, weak and jerky. Eventually the respiration ceases also, and asphyxia follows but is not betrayed by the usual convulsions owing to the motor impulses being unable to reach the muscles. The heart soon fails from the asphyxia and not through the direct action of the poison.

In the frog similar symptoms are seen, but here the arrest of the respiration is not necessarily fatal, as the skin carries on the exchange of gases, and recovery not infrequently occurs after two or even five days of complete paralysis. The cause of the curare paralysis was demonstrated by the classical researches of Claude Bernard and Kölliker. If the sciatic nerve of the frog be stimulated during the paralysis, no movement follows, but if the artery of one leg be ligatured before

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the application of the poison, this limb remains unparalyzed and reacts to reflex irritation, while the rest of the body is perfectly motionless. These facts can be interpreted only in one way; the paralysis is peripheral and not central, and may, therefore, be due to action either on the muscle, the nerve trunks, or the intermediate structures. That it is not due to the muscle is shown by the fact that direct stimulation causes the same movement as usual. On the other hand, in the experiment in which the artery is ligatured, stimulation of the nerves above the ligature, that is, where the poison has access to the nerve fibers, causes contraction, so that the nerve trunks do not seem affected. This may be shown in another way; if a nerve-muscle preparation be made, and the nerve be laid in a solution of curare, contraction of the muscle still occurs on stimulation of the nerve, but if the muscle be laid in the curare solution stimulation of the nerve has no effect, while direct stimulation still causes contraction. Curare, therefore, acts on the connection between the nerve and muscle within the muscle itself and paralyzes it without previous stimulation.

Action on Nerve-ends.—Since the investigations of Bernard and Köllicker, the action of curare has been known to be peripheral, and it was for a long time assumed that it could be localized in the hypothetical structure known as the motor end-plates. However, the action of nicotine on the muscles is opposed by curare, not only in normal muscles, but also in those in which the nerves and nerve-endings have degenerated through section. The action of curare here must be exerted, not on any end-plate, but on some undegenerated substance, which has been termed the myoneural junction and which normally serves to transfer the nerve impulse by means of a chemical intermediary substance, from the nerve-plate to the actual contractile substance of the muscle.

Although the condition of "paralysis" produced by these poisons is superficially analogous to that termed by physiologists "fatigue," the two conditions are fundamentally different. Thus neostigmine and acetylcholine increase the response of curarized muscle to indirect stimulation but lessen the response of normal and fatigued muscles. Epinephrine also is more effective as a decurarizing agent than it is against fatigue (Rosenblueth, *et al.*).

If acetylcholine is the chemical mediator between the nerve impulse and the skeletal muscle, then it is possible to explain the action of curare as being due either to an impairment of acetylcholine production or to its preventing the action of the acetylcholine upon the muscle. The decurarizing agents such as physostigmine, neostigmine and acetylcholine either antagonize or overcome these possible actions of curare. If, for example, the curare makes the muscle relatively impermeable to the acetylcholine, an additional amount of this chemical would raise its concentration and thus overcome the block. Physostigmine on the other hand might accomplish the same end by preventing the destruction of the acetylcholine and thus secure a supply sufficient to overcome the block.

Curare acts first on the nerves of the toes, ears and eyes, later on those supplying the limbs, head and neck, and, last of all, those supplying the muscles of respiration. At first slight movements can be performed, because single impulses can pass through the nerve-ends, but sustained

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contractions such as are necessary to preserve the equilibrium, cannot be maintained, and the animal therefore cannot support itself. The intermittent impulses to the respiratory muscles still allow time in the interval for the recovery of the terminations, but as the intoxication proceeds the number of impulses which can pass through becomes fewer and fewer, and the movement therefore assumes more and more the character of a jerk and eventually ceases.

Small doses do not affect the innervation of unstriped muscle, and the strict demarcation of its action is seen very distinctly in organs which consist partly of striated and partly of unstriated fibers. Thus in the esophagus, the striated muscle fibers no longer contract on stimulation of the vagus after curare, while the unstriated continue to respond as usual. In the iris of the mammals, which consists of unstriated muscle, curare has no effect, while the striated muscle of the bird's iris ceases to respond to stimulation of the motor oculi, but contracts on direct stimulation. The terminations of the nerves in the heart are not affected, but the nerves of the lymph hearts of the frog are paralyzed. The nerve-ends in striated muscle in invertebrates appear to be immune to curare (Straub). The nerve fibers seem unaffected by curare, for stimulation causes the usual electrical changes in them.

The Autonomic Sympathetic Ganglia are paralyzed by large doses, and stimulation of the preganglionic nerve fiber has no effect, nor does injected acetylcholine affect the ganglia after curare although in the intact animal acetylcholine still stimulates the postganglionic endings. For example, stimulation of the vagus does not slow the heart, and stimulation of the chorda tympani does not cause secretion, because the impulses fail to pass the ganglia on their course. The terminations of the postganglionic fibers are apparently not affected, for stimulation beyond the ganglia has its usual effect.

The peripheral terminations of the afferent or sensory nerves seem unaffected, for if the artery of one leg be ligatured before the application of curare, reflex movements may be obtained in it from stimulation of any part of the body, while if the sensory terminations were paralyzed, reflexes could be elicited only by the irritation of parts to which the poison had not penetrated, *i. e.*, from the ligatured leg.

The central nervous system is stimulated by large quantities of curare, and when it is applied directly to the brain and cord without reaching the muscles, it causes violent spasms (McGuigan), which appear to resemble those of the picrotoxin series rather than those induced by strychnine. The heart is not directly affected, but large quantities may paralyze the vagus ganglia and release the heart from inhibition. At the same time the blood-pressure may fall from paralysis of the ganglia on the vasoconstrictor nerves. The movements of the intestine, spleen and other organs are sometimes accelerated through a similar paralysis of the ganglia on inhibitory nerves.

Metabolism.—The cessation of the ordinary movements after curare and under artificial respiration naturally reduces the metabolism, but if the temperature is kept up by the external application of heat, the tissue change is not arrested in the muscles, and the CO_2 excretion and O_2

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absorption are only slightly lower than those of the unpoisoned animal at rest. Sugar and lactic acid are often found in the urine after curare, but this is due to partial asphyxia and not to the direct action of the poison; the glycogen of the liver and muscles disappears from the same cause.

Curare is **excreted** by the kidneys apparently unchanged. It has long been known that this arrow poison may be swallowed with impunity, provided there is no wounded surface in the mouth or throat, and that it is therefore perfectly safe to suck the poison from a wound. This has been explained by assuming that the absorption from the stomach is so slow that the kidneys are able to excrete the poison as fast as it reaches the blood and that this prevents its accumulating in sufficient quantity to affect the tissues.

The characteristic action of curare on the myoneural junction in striated muscle is antagonized to some extent by physostigmine, nicotine, and particularly by neostigmine which is the best antidote for clinical use. The paralyzing effect of curare on the isolated muscle of the toad is also largely inhibited by the addition of calcium to the Ringer solution, or in case paralysis had taken place it is almost completely removed by the use of calcium (Feng).

Potassium, too, has been shown by Wilson and Wright to exert an anti-curare effect although the antagonistic action is of a somewhat temporary character. Like neostigmine, potassium has little effect upon the fatigued muscle, thus indicating again that there must be a fundamental difference between a fatigued and a curarized muscle.

Therapeutic Uses.—The muscular paralysis produced by curare early suggested its use in convulsive conditions such as tetanus, tetany, strychnine poisoning, etc. The possibility of its therapeutic use depends largely upon whether an adequate degree of muscular relaxation can be obtained without arrest of respiration, and therapeutic experiments have been hampered by the difficulty of obtaining reliable preparations of curare, or of its active principles. This has been made possible by the introduction of intocostrin to be discussed next.

INTOCOSTRIN

Intocostrin, a preparation containing the therapeutically desirable constituents of curare, has recently been introduced into therapeutics and has found several fields of application. It is prepared from the bark and stems of Chondodendron tomentosum and assayed on rabbits by noting the dose required to make it impossible for the animal to raise its head. The provisional unit is equivalent to the potency of 0.15 mg. of *d*-tubocurarine chloride. Intocostrin has been used in the shock therapy of mental disorders to reduce the severity of the convulsions which often cause fractures of the spine. It has also been used in conditions of spasm, tremor, athetosis, and rigidity of voluntary muscles in certain neurologic conditions and in the diagnosis of myasthenia gravis. Its most important use has been as an adjuvant to anesthesia to increase muscular relaxation and thus allow the amount of anesthetic and the depth of anesthesia to be decreased (*cf.* page 309).

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When used in shock therapy intocostrin is administered in doses of 0.5 unit per pound of body weight intravenously. In spastic and athetoid states 0.5 to 1.5 units per pound of body weight is administered intramuscularly at four day intervals. As a diagnostic agent in myasthenia gravis, about one-tenth of the average dose is administered intravenously followed in two to three minutes by an intravenous injection of 1.5 mg. of neostigmine methylsulfate and 0.65 mg. of atropine sulfate. As an adjuvant in anesthesia 40 to 60 units are administered when the skin incision is made with the addition of 20 to 30 units later if needed.

In case of failure of the respiration, 2 cc. of a 1:2000 solution of neostigmine is injected intravenously and artificial respiration instituted until the curare effect has diminished.

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OTHER CURARIZING DRUGS

Paralysis of the terminations of the motor nerves in striated muscle —the so-called "Curare-Action"—is elicited by a large number of poisons, but in few of them is it the first effect of their application. Many drugs induce it only when injected in large quantities and at the end of a series of phenomena produced by their action on other parts of the body; it is observed much more frequently in frogs than in mammals, and is often of little importance compared to the other symptoms. Among the bodies which resemble curare more closely in their action, the peripheral paralysis playing the chief rôle in their effects, are the ammonium compounds formed from the natural alkaloids by the substitution of an alkyl, *e. g.*, methylstrychnine, amylquinine, etc. Some of the ammonium salts and many of the alkyl combinations of ammonium, phosphorus, arsenic and of several metals, also cause it. The tetraethyl ammonium salts have a much weaker curariform action than the tetramethyl compounds, and unlike the latter produce an initial increase in excitability accompanied by fibrillary twitches. Of greater practical importance is the fact that the venom of the Cobra and of other colubrine snakes has the same point of action as curare, from which it differs in

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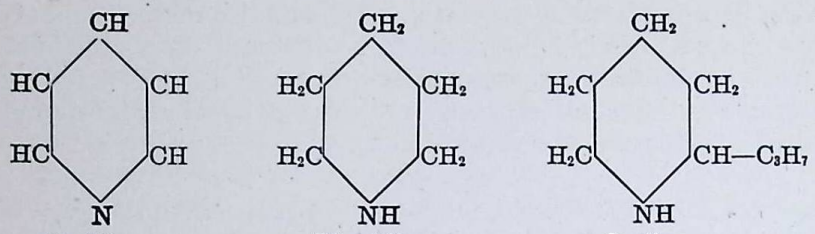
the slowness of its action and the tenacity with which it holds the nerve ends. The toxin of botulism, a form of food poisoning, has also been shown to paralyze nerve terminations.

Coniine.—A series of alkaloids may be formed from piperidine by substituting methyl, ethyl, propyl or other alkyls for hydrogen, and one of these, propyl-piperidine, is the natural alkaloid coniine and was the first alkaloid to be formed synthetically.



Pyridine **Piperidine** **Coniine**

Coniine is found in Hemlock (Conium maculatum), along with two nearly allied alkaloids, *Methylconiine* and *Conhydrine*. The action of these and of the other simple piperidine compounds resembles that of coniine, but is much weaker.

Symptoms.—The general symptoms induced in man by poisonous doses of coniine are weakness, languor and drowsiness which does not pass into actual sleep. The movements are weak and unsteady, the gait is staggering, and nausea and vomiting generally set in, along with profuse salivation. In most cases the intelligence remains clear to the end, as is related of the death of Socrates from hemlock poisoning, but in some instances imperfect vision and hearing have been noted. The pupils are somewhat dilated. Tremors and fibrillary contractions of the muscles are often seen in animals, and some observers state that actual convulsions occur. The breathing becomes weaker and slower and death occurs from its arrest.

Gelsemium.—Gelsemium sempervirens (Yellow Jasmine or Carolina Jasmine) contains several alkaloids which have not yet been fully separated and identified. A crystalline alkaloid, gelsemine, $C_{20}H_{22}O_2N_2$, is inactive in mammals but produces strychnine-like convulsions in frogs. "Gelseminine," an amorphous alkaloid which was shown by Cushny to be highly poisonous to mammals and believed to be the active principle, is regarded by Sayre as a mixture of three alkaloids, to which the names sempervirine, gelsemidine and gelsemoidine were given. Chou has isolated gelsemicine ($C_{20}H_{25}O_4N_2$) which is highly toxic to mammals, and he considers that the poisonous nature of gelsemium is due to the presence of gelsemicine, sempervirine and possibly other amorphous bases.

The symptoms of gelsemium poisoning resemble closely those of coniine, in man the chief symptoms being double vision, ptosis, dilatation of pupils, increasing muscular weakness affecting speech and gait, and final arrest of respiration.

Sparteine.—Another alkaloid which resembles coniine closely in its action is *Sparteine*, which is found in the common broom plant (Spartium or Cytisus scoparius), and in various species of lupines. It is a pyridine derivative possessing the formula $C_{15}H_{26}N_2$, and is a fluid, but forms crystalline salts.

Action.—The general effects of sparteine are almost identical with those of coniine, but it seems very probable that the central nervous system is little affected by it, the whole of the phenomena pointing to a paralysis of the motor nerve terminations and of the sympathetic ganglia. Sparteine has more effect than coniine on the heart, which it depresses, so that the rhythm is slow and the contractions weak.

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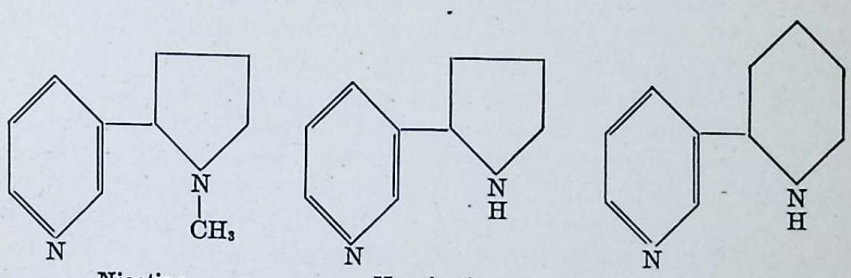
E. SUBSTANCES ACTING ON THE AUTONOMIC NERVOUS SYSTEM

I. NICOTINE GROUP

Nicotine, the well-known alkaloid of tobacco (*Nicotiana tabacum*), is a volatile fluid, possessing a strong alkaline reaction, and forming salts with acids, most of which are amorphous. It is a combination of pyridine with methylpyrrolidine as shown in the accompanying formulæ:



Nicotine Nornicotine Anabasine

Nicotine is the only constituent of tobacco which possesses any toxicological interest, although several other alkaloids are present in comparatively small amounts. It is accompanied by a volatile oil in dried tobacco, but this is only developed during the processes of preparation and seems to have no action apart from that of the other volatile oils. The odor and flavor, and probably the "strength," of tobacco depend in part upon the quantity and quality of this oil, in part on some products of the decomposition of nicotine. Absolutely pure nicotine has comparatively little odor, but it decomposes when kept, becomes dark colored, and acquires the characteristic odor of tobacco. Naturally occurring nicotine is levorotatory and is twice as active biologically as the synthetic dextrorotatory product.

The pituri plant (*Duboisia Hopwoodii*), the leaves of which are used by the Australian natives in the same way as tobacco by the civilized races, contains as its chief alkaloid nornicotine, which has similar actions to nicotine which it resembles in structure, lacking only the methyl group in the pyrrolidine nucleus which is replaced by a hydrogen atom. *Anabasine*, with actions similar to nicotine but weaker, has been isolated from *Anabasis aphylla* (Chenopodiaciæ), a native of Central Asia. It consists of a piperidine ring in combination with pyridine. Lobelia inflata, or Indian tobacco, contains several alkaloids, one of which, *Lobeline*, resembles nicotine in many of its actions. *Cytisine* ($C_{11}H_{14}N_2O$), the alkaloid of laburnum (*Cytisus laburnum*), gorse and other plants, also resembles nicotine very closely in action. A congener of cystisine, called Anagyrine, has been isolated from *Anagyris fœtida*. Another body with the same type of action is the artificial quaternary ammonium base, *Methylhordenine*.

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Symptoms.—Poisonous doses administered to man or other mammals cause a hot, burning sensation in the mouth, which spreads down the esophagus to the stomach, and is followed by salivation, nausea, vomiting, and sometimes purging. The breathing is quick, deep and labored, and is often accompanied by moist râles. The pulse is generally slow and sometimes weak at first, and then becomes very rapid, but after very large doses may be first accelerated and then slow and feeble. Some mental confusion, great muscular weakness, giddiness and restlessness are followed by loss of coördinating power and partial or complete unconsciousness. Clonic convulsions set in later, accompanied by fibrillary twitching of various muscles, and eventually a tetanic spasm closes the scene by arresting the respiration. In other instances the convulsions are followed by collapse with complete relaxation of the muscles, the reflexes disappear, the respiration becomes slow and weak and finally ceases, the heart continuing to beat for some time afterwards. Very large doses of nicotine may prove fatal within a few seconds; the symptoms are those of sudden paralysis of the central nervous system, including the respiratory center, and no convulsions are developed. Nicotine is about as poisonous as hydrocyanic acid.

In the frog the same excitement and violent convulsions are seen as in mammals, but the respiration soon ceases, and there follows a "cataleptic" stage in which the animal assumes a characteristic attitude. The fore-legs are crossed in front of the sternum and are rigid, the thighs are at right angles to the axis of the body and the legs are flexed on them but are not rigid. When a leg is drawn down it at once returns to its original position, and the frog still attempts to escape when it is aroused. Fibrillary contractions are observed in many of the muscles. Somewhat later, the reflexes disappear, the muscles become flaccid, and eventually complete paralysis occurs from a peripheral, curare-like action.

Nicotine has but little toxic action on the lowest invertebrates, but as the nervous system begins to be differentiated it causes paralysis, and still higher in the scale the paralytic action is preceded by a stage of stimulation.

In the treatment of nicotine poisoning, artificial respiration should be instituted since death occurs usually as a result of failure of respiration due to paralysis of the respiratory muscles.

Actions.—The actions of nicotine are very complicated, for it has at least three sites of action, on each of which it produces a primary stimulation followed by paralysis. These sites are: the central nervous system, all autonomic ganglia, and the nerve-ends in voluntary muscle. Nicotine may, for example, affect the circulation through the vasomotor and vagus centers as well as through the sympathetic and parasympathetic ganglia, in each case with the possibility of stimulation and paralysis. The resultant effect on the heart-rate and blood-pressure will, therefore, vary with the dose. It is modified also by the species of animal, the anesthetic used, and the integrity of the central nervous system.

The action on autonomic ganglia, especially the paralyzing effect of

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large doses, is often referred to as a nicotine action. After such a dose, stimulation of a preganglionic fiber fails to produce the usual action, as the path of the stimulus through the ganglion is interrupted. Stimulation of the postganglionic fiber by chemical or electrical stimulus will, however, still produce the characteristic effect. Nicotine acts in this way on all autonomic ganglia that have been investigated.

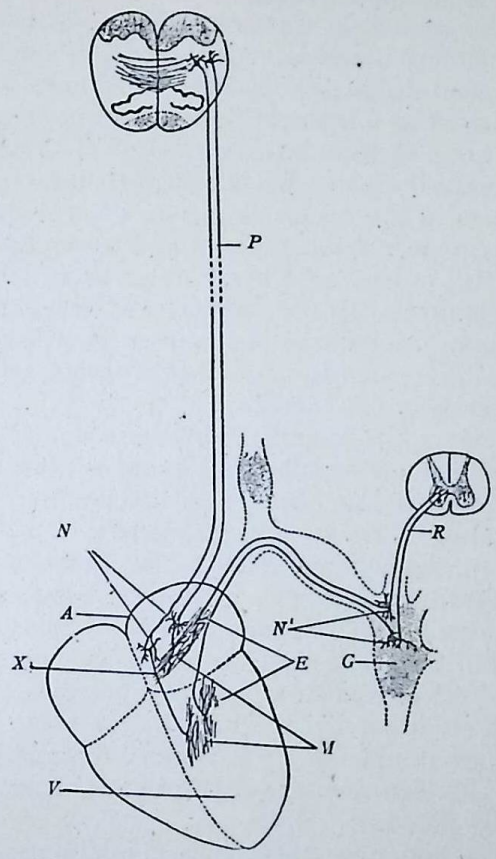

FIG. 32.—Diagram of the regulating nerves of the heart. *P*, inhibitory parasympathetic fibers (vagus), terminating around ganglion cells in the auricle (*A*). The axis cylinders issuing from these cells terminate on the muscular fibers of the auricle and ventricle (*V*). *R*, accelerator sympathetic fibers terminating around ganglion cells in the stellate ganglion *G*. The axis fibers of these ganglion cells run through the *Annulus Vieussenii* and terminate on the muscular fibers of the auricle and ventricle. *N*, *N'* points at which *nicotine*, *coniine*, *curarine*, etc., act—the ganglion cells surrounded by the terminations of the nerves. *M*, points at which *muscarine* and *atropine* act—the terminations of the postganglionic fibers which arise from the intracardiac ganglia on the parasympathetic path. *E*, points at which *epinephrine* acts—the myoneural junction on the sympathetic path.

The action of nicotine on the ganglion cells made it possible for Langley in his classic experiments to differentiate those nerve fibers which pass through a given ganglion without synapsing from those in which the preganglionic fibers end in a synapse within the ganglion. It is only the latter which are affected by nicotine. Hence, if the application of nicotine to a ganglion blocked an impulse, it could be assumed that the fiber carrying this impulse had a synapse in the ganglion.

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Nicotine in first exciting and then paralyzing the ganglia does not affect the release of the chemical mediator (acetylcholine) at the cholinergic (preganglionic) nerve ending but exerts its action directly on the ganglion cells.

The fact that nicotine exerts both stimulating and paralyzing actions at multiple sites renders the pharmacological effects which follow its administration complex and variable.

Circulation.—The action on the circulation is extremely complex, as a number of factors are involved. After moderate quantities the heart is slow and may stand still in diastole for a few seconds, but then recovers gradually and regains its former rhythm or becomes somewhat quicker. The slow pulse is due to stimulation of the ganglia on the vagus nerve (Fig. 32, *N*), exactly the same effects being produced as by stimulation of the vagus fibers in the neck. It is not affected by section of the cervical pneumogastric, as the path from the ganglia to the cardiac muscle fibers is still intact, but on the other hand, it is prevented by atropine, which paralyzes the terminations of the postganglionic fibers, and therefore blocks the passage of impulses from the ganglia to the muscle. It is also prevented by a number of drugs, such as curare and coniine, which paralyze the ganglia.

This stimulation of the ganglia is of short duration, soon passing into paralysis, so that on stimulating the vagus after nicotine there is no slowing of the heart but often some acceleration, due to the fact that the accelerating fibers running along with the inhibitory in the vagus nerve are postganglionic fibers to the heart, and are therefore unaffected by nicotine. Although inhibitory impulses can no longer reach the heart from above, stimulation of the venous sinus in the frog still causes arrest of the heart, since the stimulating current here reaches the inhibitory nerves beyond the paralyzed ganglia (Fig. 32, *X*), and these preserve their usual irritability. In the same way muscarine, which acts upon the postganglionic inhibitory terminations in the heart muscle (Fig. 32, *M*), can slow the rhythm even after the ganglia have been paralyzed by nicotine.

In addition to its action on the peripheral inhibitory ganglia, nicotine seems to stimulate the vagus center in the medulla, as the slowing is greater when the vagi are intact than when they are divided. But apart from this action on the inhibitory apparatus, nicotine also at first stimulates the ganglia on the accelerator fibers, so that when the inhibitory mechanism has been put out of action by atropine, moderate quantities of nicotine increase the rate. Larger amounts paralyze the accelerator ganglia (*N′*, Fig. 32) and thus tend to slow the heart. A further action is said to be exercised on the heart muscle itself, which is first stimulated and then depressed (Wertheimer).

On the injection of nicotine into a vein or subcutaneously, an immense augmentation of the arterial tension occurs; this is due in part to stimulation of the vasoconstrictor center in the medulla, in part to stimulation of the ganglia on the course of the vasoconstrictor nerves.

The constriction of the vessels can be observed in many parts of the body—mesentery, foot, rabbit's ear, etc. In these parts the pallor produced by the

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narrowing of the vessels is followed by redness and congestion owing to the paralysis of the ganglia, and at the same time the pressure falls to a level somewhat below the normal. In some parts of the body no constriction of the vessels occurs; for example, the dog's lip and mouth are congested first and then become pale. This flushing seems partly due to the stimulation of the ganglionic apparatus on the vaso-dilator fibers for the lips and mouth, and partly to the constriction of the vessels in the splanchnic area diverting the blood current to those parts which are less abundantly supplied with constrictor fibers, for it occurs after removal of the superior cervical ganglion containing the vasodilator fibers.

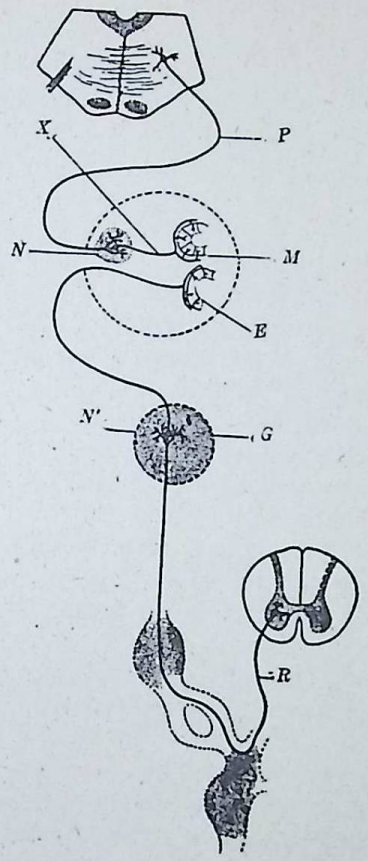

FIG. 33.—Diagram of the innervation of the submaxillary gland. *P*, parasympathetic fibers (chorda tympani), terminating around a ganglion cell in the hilus of the submaxillary gland. The axis from this ganglion cell runs to the secretory epithelium. *R*, sympathetic fibers. terminating around a ganglion cell in the superior cervical ganglion *G*. The axis from this cell runs to the secretory epithelium. In the diagram the nerves are represented as running to separate acini. *N*, *N'*, ganglion cells surrounded by the terminations of the nerves—the points at which *nicotine* acts. *M*, the terminations of the secretory fibers connected with the chorda tympani—the points at which *atropine*, *muscarine* and *pilocarpine* act. *E*, the terminations of the secretory fibers connected with the sympathetic—the point at which *epinephrine* acts.

After a few minutes the blood-pressure falls to the normal level or lower, but a second injection again produces a similar rise in the arterial tension, unless the first was large enough to weaken the ganglia.

In the human, the administration of 2 mg. of nicotine by injection or through the medium of smoking results in an increase in pulse rate

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and in many individuals in an increase in blood-pressure. The electrocardiogram may reveal a depression or inversion of the T wave.

Respiration.—The respiration is at first rapid and shallow with some deficiency in the expiratory movements, but after a time, while maintaining the acceleration, it becomes deeper. It is liable to be interrupted at this stage by the convulsions, but if these do not prove fatal, it gradually becomes slower while remaining deep. Later, pauses in the position of expiration appear, and the movements become weaker until they disappear, the animal dying of asphyxia. The respiratory center is first stimulated and then depressed and its failure has been believed to be the cause of death, the heart continuing to beat for some time afterwards, although slowly and weakly. The failure of the respiration is not always a result of paralysis of the respiratory center for impulses are still being transmitted through the phrenic nerve after respiratory movements have ceased. However, the curare-like action of the nicotine on the nerve endings in the diaphragm prevents the respiratory muscles from responding (Gold and Modell).

The *bronchial* muscle relaxes after a transient constriction when nicotine or lobeline is injected, these changes being brought about by stimulation of the ganglia on the course of the vagus fibers which cause contraction of the bronchial muscle, and later of those on the sympathetic fibers which cause active dilatation.

Most of the **Secretions** are increased temporarily by nicotine. The glands investigated have generally been the salivary, where it is found that the secretion is increased by the injection of small quantities, but is afterward depressed, while large doses diminish it at once. The seat of action is again the ganglionic apparatus on the secretory nerves. If the chorda tympani is stimulated in the normal animal a large secretion of saliva follows at once, but if a sufficient quantity of nicotine be injected, no such effect follows its stimulation. If, however, the nerve fibers are stimulated between the ganglion cells and the gland (at *X* in Fig. 33), the secretion again follows as before. On the other hand, nicotine increases the secretion whether the chorda is intact or not, but ceases to act if the connection between the ganglion cells and the gland is interrupted. Nicotine thus first stimulates and then paralyzes the ganglia on the course of the chorda tympani and of the sympathetic fibers supplying the gland. Pilocarpine and muscarine cause profuse salivation after nicotine because they stimulate the postganglionic terminations in the gland cells, and it is therefore immaterial whether the connection with the central nervous system be interrupted or not. On the other hand, the reflex secretion of saliva normally produced by irritation of the mouth or by chewing is prevented by nicotine. Atropine stops the secretion produced by nicotine by paralyzing the postganglionic terminations.

The other secretory glands are affected in the same way by nicotine, their secretions being first increased by the stimulation of the ganglia on the course of their secretory nerves, and then being lessened by their paralysis. Thus the secretion of sweat and bronchial mucus is found to be markedly increased. The urine and bile have not been shown

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to be affected by nicotine, as their secretion does not seem to be so dependent upon nervous influences. The activity of the suprarenal glands is increased by nicotine, probably by its action on the ganglia on the course of the innervating fibers; this results in an augmented secretion of epinephrine into the blood-vessels, which in turn affects a number of organs, such as the iris and uterus, and introduces a new complication in the action of nicotine.

Nicotine produces extreme **Nausea and Vomiting** when taken even in comparatively small quantities, a fact which is generally recognized by tyros in smoking. This is in part central in origin, in part due to the powerful contractions of the stomach walls. This contraction extends throughout the intestinal tract, so that repeated **Evacuation of the Bowel** occurs. Somewhat larger quantities may lead to a tetanic contraction of the whole intestine with almost complete obliteration of the lumen. This exaggeration of the peristaltic contraction is probably due to stimulation of the motor ganglia in the intestinal wall, and a subsequent paralysis of these structures leads to a failure of local stimuli to induce peristalsis. A further effect of nicotine on the bowel is due to its stimulating the ganglia on the fibers of the splanchnic which inhibit the rhythmical pendulum movements. These are arrested by the injection of nicotine, but return in exaggerated form as the ganglionic stimulation passes into paralysis. The mesenteric vessels are narrowed at first from stimulation of the ganglia on the course of the vasoconstrictor nerves, but congestion follows the depression of these ganglia and the blood-pressure falls.

Similar changes are produced by nicotine in the **Bladder**, which is thrown into tetanic contraction. The urine is therefore expelled very soon after the injection of nicotine and this probably gave rise to the erroneous view that the renal secretion was increased. The uterus is strongly contracted in pregnant animals, but is inhibited in the non-pregnant cat, in which the inhibitory nerves are more powerful than the contractor ones.

The action of nicotine on the **Pupil** varies in different animals, for while in the cat and dog its application either intravenously or locally produces marked but transitory dilation, in the rabbit partial constriction sets in immediately. In cases of acute poisoning in man contraction is generally seen at first and is followed by dilatation. In birds nicotine causes very marked contraction of the pupil, apparently owing to direct action on the muscle of the iris. The size of the pupil is regulated by two sets of nerves, the motor oculi and the sympathetic, and the ciliary fibers of both of these are interrupted by ganglia in their passage from the brain to the iris, those of the motor oculi by the ciliary ganglion, those of the sympathetic by the superior cervical ganglion (see Fig. 35, page 468); the varying effects of nicotine may be due to its stimulating the one ganglion more strongly in one species of animals, the other in another. It is found, however, that atropine does not remove the effects of nicotine on the rabbit's eye, which would seem to indicate an action on the muscular fibers of the iris. Several other effects on the orbital muscles are seen; thus in cats and dogs the nicti-

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tating membrane is withdrawn, the eye opens and is directed forward, while in the rabbit these symptoms are preceded by a stage in which the nictitating membrane is spread over the cornea and the eye is tightly closed; these all arise from stimulation and subsequent paralysis of the superior cervical ganglion.

Nicotine, then, first stimulates and later paralyzes all the **Autonomic Ganglia**, whether applied locally to them or injected into the circulation. In these ganglia, the characteristic formation is the basket-like arrangement of the terminations of the entering nerve, which surround a large nerve cell from which an axis cylinder runs to the muscle or secretory cell. A nerve impulse from the central nervous system passes from the basket to the cell and thence to the periphery. Langley has shown that nicotine acts on the cell of the peripheral neuron, and not on the network around it, for the same effect is obtained from the application of the poison after the network has degenerated.

In the frog nicotine produces fibrillary twitching and slow, prolonged contraction of the **Muscles**, which are not prevented by previous division of the nerves leading to them, but disappear on the injection of curare; on the other hand, the paralysis induced by curare may be partially removed by small quantities of nicotine. Langley has shown that the fibrillary twitching and slower contractions occur in muscles in which the nerve-ends have degenerated from division of the nerves, so that nicotine acts on some receptive substance peripheral to the anatomical nerve-ends and intervening between these and the contractile substance of muscle. A similar effect is seen in reptiles and birds; in mammals the twitching of the muscles is prevented by section of the nerves and is, therefore, due to central action, but large quantities of nicotine cause paralysis exactly like curare.

The convulsions seen in both cold- and warm-blooded animals evidence the influence of nicotine on the **Central Nervous System.** The spinal cord is thrown into a condition of exaggerated irritability, and the reflexes are correspondingly increased, but the convulsions do not seem to be due so much to the spinal cord as to the medulla oblongata and hind brain, for they are not tonic but clonic in character, and are much weaker after division of the cord immediately below the medulla than in the intact animal. The medullary stimulation also betrays itself in the rapid and deep respiration, and is in part responsible for the inhibitory slowing of the heart and the rise in the blood-pressure. The higher centers in the brain seem to participate but little in the stimulant action of nicotine, which is short-lived, and soon gives way to marked depression of the whole central nervous system, manifested in the slow respiration, the low blood-pressure, the disappearance of the reflex movements and the final unconsciousness.

The cause of death in nicotine poisoning has aroused considerable interest since Thomas and Franke called attention to the importance of the curare-like action of nicotine in this connection. These workers showed that sections of the diaphragm of a dog connected to the body of the animal by the phrenic nerve only, and therefore protected from the action of the poison, will remain active to stimulation of the nerve long after the intact portion of the diaphragm in the animal is paralyzed by the nicotine injected. They concluded, therefore,

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that under the conditions the death of the animal was due to a peripheral paralysis of the nerves involved in respiration rather than to a paralysis of the respiratory center. However, in order to bring about this condition of peripheral paralysis, doses of nicotine two or three times the minimum fatal doses were given (15 mg. per kilo of body weight), and the problem still remains as to the cause of death from the smaller doses which really constitute the minimum fatal dose.

Without doubt a curare-like action may be a cause of death from nicotine. However, the evidence that the early death which follows the administration of small doses of nicotine to normal unanesthetized animals is not due to depression of the respiratory center is not sufficiently established to be finally accepted.

The **Excretion** of nicotine is probably carried on mainly by the kidneys, for it is found in the urine very soon after it enters the blood. It has also been detected in the saliva and perspiration. The presence of nicotine in the urine of smokers may account for its pressor activity for nicotine is only slowly excreted from the body.

When small quantities of nicotine are ingested repeatedly, the body soon gains a certain **Tolerance**, and no symptoms whatever are produced by doses which in ordinary cases would produce grave poisoning. A familiar example of this tolerance is seen in the practice of smoking. The first use of tobacco in the great majority of individuals is followed by vomiting and depression, which may even amount to collapse, but after a few experiences no symptoms follow smoking. In some individuals no such tolerance is developed, and in every case the tolerance is much more limited and more difficult to acquire than that for morphine. In animal experiments it is often found that while one application of nicotine produces considerable ganglionic stimulation, the second has much less effect. This is probably due, not to the establishment of tolerance, but to the first dose having produced primary stimulation and then depression of the ganglia, this depression, while not amounting to complete paralysis being sufficient to counteract to some extent the stimulant action of the second injection. True tolerance is attained very imperfectly by animals from the use of repeated small doses, but when larger amounts are used some tolerance is soon acquired. Animals which have acquired tolerance for nicotine also resist the action of lobeline. Certain animals have a natural tolerance against nicotine, this being strongest in rabbits. In diminishing degree appear guinea-pigs, dogs, hens and finally cats where this congenital tolerance is least.

Therapeutic Uses.—Lobelia was formerly used as an emetic, but is unreliable, and is liable to give rise to the most alarming symptoms of poisoning. It is occasionally used in the form of the tincture (dose, B. P., 5 to 15 min.), to relax the spasm of the bronchial muscle in asthma, but its effects must be carefully watched, as the preparations seem to vary in strength, and alarming symptoms and even fatal results have sometimes followed its use. In any case it is inferior to atropine and its allies in this condition. The British Pharmacopœia also includes a concentrated ethereal tincture of lobelia, the dose of which is 0.08 to 0.25 mil ($1\frac{1}{3}$ to 4 min.). *Lobeline* stimulates the respiratory center and has been used for this purpose in respiratory failure occurring during anesthesia, in narcotic poisoning and similar conditions, but safer and more effective drugs are available for this purpose. It is usually given hypodermically in doses of 3 to 10 mg. Nicotine is not used in therapeutics, but is a very useful tool in experimental pharmacology.

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Tobacco

Tobacco had been in use among the aboriginal tribes of America before they became known to civilization. It was introduced into Europe soon after the discovery of America, and its use as an article of luxury, beginning in England, soon spread to the continent, and in spite of papal bulls and numerous efforts on the part of the secular authorities, has continued to enthrall a considerable portion of the human race. The most widespread use of tobacco—smoking—is also the most ancient one, having been that of the aboriginal Indians. Snuff-taking, introduced by Francis II of France, remained fashionable for a long time, but is now almost obsolete except in remote rural areas. Tobacco-chewing is a more modern development, but shows signs of abatement. Curiously enough, the leaves of the pituri plant, which contains nicotine, are formed into a mass and chewed by the natives of Australia. In smoking, snuffing or chewing, nicotine is absorbed; tobacco smoke always contains nicotine, though the amount varies with different kinds of tobacco and also with the way in which it is smoked; but a large proportion of that contained in tobacco passes over in the smoke along with pyridine and some of its derivatives. In snuff the nicotine is generally small in amount, while in chewing tobacco there is generally a varying amount of foreign matter, such as molasses.

The enjoyment derived from the use of tobacco has never been adequately explained, and it is not even proved that nicotine is essential to the pleasurable results, though there seems little doubt that it plays an important part in producing them. It has been suggested that smoking gives repose and thereby improves intellectual work, but this is denied by many habitual smokers. It has also been stated, and denied, that the mental energy is reduced by the use of tobacco, and an attempt has been made to demonstrate this by measuring the amount of work done with and without tobacco; but investigators are not agreed on the results, which probably depend largely upon the individual. One fact is certain, that the tobacco habit cannot be compared with the use of such drugs as morphine, cocaine, or alcohol, for it is not taken with the purpose of producing stimulation or depression of the central nervous system, and it seems doubtful whether the nicotine ordinarily absorbed really has any action whatsoever. Perhaps the local effects on the mouth, nose, and throat play a larger part in the effects of tobacco than is generally recognized. A certain amount of rhythmic movement demanding no exertion seems in itself to have a soothing, pleasure-giving effect, for it is otherwise impossible to explain the satisfaction enjoyed by many in chewing tasteless objects, such as gum or straws. A curious fact which tends to show that tobacco smoking is not carried on solely for the sake of the nicotine absorbed, is that the pleasure derived from a pipe or cigar is diminished for many persons if the smoke is not seen, as when it is smoked in the dark; and few blind men enjoy smoking.

Most people may indulge in the moderate use of tobacco for many years with perfect impunity, but its excessive use is followed in many

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individuals by a number of symptoms, some of them trivial, others indicating grave changes in important organs.

One of the commonest effects of overindulgence in tobacco is a chronic inflammation of the throat and upper parts of the respiratory passages, leading to hoarseness and excessive secretion of the mucous glands. This is explained by the constant application to the throat of an irritant, alkaline vapor, and is probably not due to the specific action of nicotine. A similar irritated condition of the tongue is frequently met with, more especially when the hot vapor is constantly directed on one part, as in pipe smoking, and it is sometimes stated that the constant irritation thus produced renders the tongue and lip more liable to cancerous disease. The apparent increase in the incidence of carcinoma of the lung has also been attributed to the increasing use of tobacco. Dyspepsia, want of appetite, and consequent loss of flesh may also be explained by the local irritation produced by the nicotine swallowed in the saliva. A symptom ascribed to the abuse of tobacco is palpitation and irregularity of the heart, which has been attributed to changes in the inhibitory mechanism. Excessive smoking is also alleged to be a cause of coronary atheroma, but the evidence for this view is not convincing. Another important symptom is dimness of vision, especially for colors, and imperfect accommodation, which may go on to complete blindness in one or both eyes. In early cases the retina often appears pale, and if the condition persists, atrophy of the optic nerve may result, probably following on degenerative changes in the ganglion cells of the macular region of the retina. This tobacco amblyopia is held by some to occur only when the tobacco habit is accompanied by alcoholic excess, and is especially liable to occur from smoking heavy pipe tobaccos. Smoking causes a slight rise of blood-pressure in some individuals, and this has aroused apprehensions that it may tend to favor arteriosclerosis, but the change is slight and the evidence that smoking predisposes to arteriosclerosis is not convincing. Nervous symptoms, such as tremor, exaggeration of the reflexes, headache and giddiness, are sometimes developed in workmen in tobacco factories, and may be induced to a less extent by smoking or chewing tobacco. In the great majority of cases of chronic tobacco poisoning, the symptoms disappear on abandoning the habit, or even on restricting the daily consumption. The habit of smoking does not make insistent demands on its continuance as does morphine. Withdrawal of tobacco from those accustomed to it causes a temporary feeling of loss and possibly some impairment of mental concentration. This soon disappears and is not markedly greater than occurs from the discontinuance of any established pleasurable habit.

Pearl has made a statistical study of several thousand persons to ascertain if possible the effect which moderate or heavy smoking has upon longevity. Comparing the smokers with 2,000 non-smoking controls, he found that smoking impaired life duration and that the degree of impairment increased with the amount used. It is interesting to note that Pearl found that the difference between the two groups of smokers and non-smokers disappeared at the age of seventy, probably due to the "expression of the residual effect of heavily selective character

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on the mortality in the earlier years." Individual smokers who survive seventy are probably so resistant that thereafter tobacco does them no harm.

The widely prevalent view that smoking increases the volume and acidity of the gastric secretions has not been confirmed experimentally (Schnedorf and Ivy). However, the injection of 0.2 mg. of nicotine (the approximate equivalent of smoking a cigarette) reflexly abolishes the hunger contractions of the stomach for fifteen to sixty minutes.

The vasospastic action of nicotine has suggested that smoking may precipitate anginal attacks in patients suffering from angina pectoris. The use of tobacco has also been held to be the cause of Buerger's disease (thromboangiitis obliterans) but rarely cases of this disorder have been noted in non-smokers. The vasoconstricting effect of tobacco on the skin has been demonstrated by the fall in skin temperature which occurs in most normal persons following the use of tobacco.

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II. SUBSTANCES STIMULATING PARASYMPATHETIC ACTIVITY

The group of drugs now to be considered have the common pharmacological action of stimulating the structures innervated by cholinergic nerves and are therefore designated as parasympathomimetic drugs. The individual drugs differ, however, in the mechanism and site of their action as well as in their effects on different organs, and hence must be considered separately.

1. The Muscarine Group

Muscarine is an alkaloid found in certain poisonous mushrooms, especially Amanita muscaria (*Agaricus muscarius*). The alkaloid was first isolated, and its pharmacological properties described by Schmiedeberg and Koppe in 1869. Chemically, it is a quaternary ammonium

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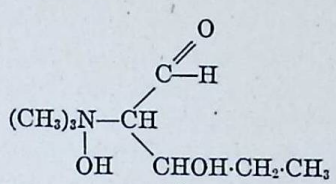
base and may be considered as the aldehyde of he secondary propyl alcohol derivative of choline (*cf.* page 444), and resembles in its actions some of the choline esters. It produces a series of effects which reproduce with almost complete fidelity the effects which result from stimulation of the parasympathetic nerves and this action is exerted on the periphery in connection with the postganglionic nerve terminations. This particular type of action, which is now known to occur with several other drugs, was first described with muscarine and is frequently and for convenience called a "muscarine action." Few other substances possess this action with the same purity as muscarine, many (*e. g.*, acetylcholine) combining with it a "nicotine action." Both for historical reasons and for simplicity, it is convenient, therefore, to consider muscarine first as an introduction to this group of drugs.



Muscarine

Actions.—Research in recent years has tended to confirm the conception that, in its peripheral actions, muscarine stimulates the postganglionic terminations of the parasympathetic nerves. When circulating in the blood, or when applied locally to organs, it therefore produces all the effects associated with stimulation of these nerves. The apparent exceptions to this generalization, notably the sweat glands, are explained by the fact that the nerves supplying these, though belonging anatomically to the sympathetic system, belong physiologically to the parasympathetic system. The stimulation of the sympathetic nerves to these glands causes the liberation of acetylcholine, and not—as is usual with sympathetic fibers—of a substance like epinephrine. If all nerve fibers which transmit their impulses through liberation of acetylcholine be designated as "cholinergic," muscarine is more accurately described as stimulating all cholinergic nerve-terminations.

The salivary and lacrimal **Glands**, the mucous glands of the mouth, throat, nose and deeper respiratory passages, the gastric secretory glands, the pancreas, and probably the intestinal glands, all secrete copiously after muscarine. The sweat glands and the ceruminous glands of the ears are likewise roused to unwonted activity, and many other glandular structures are also stimulated.

In most cases the solids of the secretions are increased as well as the fluids, although to a somewhat lesser extent. The bile, the urine and the milk do not seem to be affected directly although they may be reduced in amount or otherwise modified by the withdrawal of large quantities of fluid from the body by other channels.

After a small quantity of atropine, muscarine in ordinary quantities produces no increase in any of the secretions. This indicates that the seat of action of these poisons is not the secretory cells, for it has been

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shown that atropine paralyzes only the myoneural junctions and leaves the cells uninjured.

Involuntary Muscle.—The nausea and discomfort in the *stomach*, followed by retching and vomiting, which form some of the earliest symptoms of muscarine poisoning are a result of stimulation of the smooth muscle of the gastro-intestinal tract. The *intestines* are also set in unusually active movement by stimulation of the vagal terminations and repeated evacuation of their contents follows. These are at first of firm consistency, but later, as the continued peristalsis carries down the contents of the small intestine, which have not lain long enough in the bowel to allow of the absorption of their fluid, the feces contain more water than usual. This fluidity of the stools may also be due in part to an augmentation of the intestinal secretion. Even after the bowel has been completely evacuated, the persistent peristalsis betrays itself in painful straining.

The muscle of a number of other organs contracts from stimulation of receptors similar to those in the stomach and bowel. Thus the *spleen*, *bladder*, *ureters*, and pregnant *uterus* are contracted, and in the case of the bladder repeated evacuation and straining may occur.

In some other forms of muscle, muscarine causes contraction by acting on receptors which lie on the path of the nerve impulses. Thus in poisoning and also on local application, the *pupil* becomes extremely narrowed, and at the same time the *ciliary muscle* contracts so that the lens is accommodated for short distances. Both of these phenomena are due to stimulation of the myoneural junctions in the intra-ocular muscles (Fig. 35, page 468), for atropine removes the contraction and at the same time interrupts the passage of impulses from the nerve to the muscle. The intraocular pressure is reduced by muscarine although it may be increased at first. This is due to the iris being drawn up by its contraction and thus allowing free egress to the intra-ocular fluids (see Atropine, page 469).

The *bronchial muscles* are contracted, an effect which, together with the profuse bronchial secretion, may cause embarrassment of respiration.

The action on the **Circulation** induces symptoms which are exactly those seen on stimulation of the vagus by electrical shocks. The point of action is not the ganglia on the inhibitory fibers, for muscarine is effective after these are completely paralyzed by nicotine, and it also acts on the apex of the frog's ventricle, in which no ganglia whatever have been found. The action must therefore be localized at some point between the ganglia and the actual contractile substance, for the latter maintains its normal character responding with contractions to stimuli. Muscarine is therefore generally held to stimulate the myoneural junctions between the inhibitory fibers and the contractile substance of the muscle. Atropine removes this standstill by paralyzing the junctions, but larger quantities of muscarine will again overcome the atropine action and restore the standstill or, at any rate, the slow beat. Digitalis and its allies remove the standstill by increasing the irritability of the muscle until the inhibition can no longer hold the heart in check, but through the rhythm caused by these the activity of the vagus can be

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seen in the slowness of the beat and the prolongation of the diastole. When the heart is slowed by muscarine, stimulation of the vagus is more effective than normally, the action of the drug being added to that of the electrical stimulus. In rabbits and cats the heart is slowed or brought to a complete standstill, the blood-pressure falls, and all the symptoms produced by anemia of the brain may follow, but the animal becomes again perfectly normal on the administration of small quantities of atropine.

In dogs the stimulation of the inhibitory fibers seems sometimes to be entirely absent after muscarine, and in man this is very frequently the case. Instead of a slow pulse and lessened tension of the arteries, acceleration and increased blood-pressure are then observed. This is accompanied in man by marked palpitation and discomfort in the region of the heart and by dilatation of the skin vessels, especially of those of the face. In other cases, however, the same circulatory disturbances are produced as in the cat and rabbit. The acceleration of the heart and palpitation may perhaps arise from the nausea, which may be sufficient to overcome the inhibitory stimulation, or may result from stimulation of the adrenal glands leading to an outpouring of epinephrine.

In embryo hearts muscarine, in ordinary quantities, produces no change whatever during the first one hundred and fifty hours of life (in the chick). The explanation of this phenomenon is that the inhibitory nerves have not been developed at this stage, and after their development is complete, muscarine acts on the heart as in the adult. The absence of slowing in some of the invertebrates may be due to a similar cause, although this does not hold good for the crab, in which there is a well-defined inhibitory apparatus but in which muscarine causes acceleration.

The **Respiratory** center is not acted on directly by small quantities of muscarine, but the changes in the circulation lessen the amount of blood passing through the lungs, and the contraction of the bronchial muscle may seriously retard the movement of the air and thus impair the aeration of the blood. The edema of the lungs which is often observed in cats and rabbits poisoned with the members of this series, and which has also occurred in fatal poisoning in man, arises from the slowing of the circulation through the lungs from the cardiac action.

Muscarine has practically never been introduced into medical practice, because, while its action on the secretions is quite equal to that of pilocarpine, the gastric symptoms are produced more readily by it. It is also a more powerful poison than pilocarpine, and is not procurable in pure form.

Toxicology.—The symptoms of poisoning in man commence with a very marked secretion of saliva, soon followed by excessive perspiration and a flow of tears. Nausea, retching and vomiting, pain in the abdomen and violent movement of the intestines causing profuse watery evacuations, are next observed. The pulse is sometimes quickened, sometimes very slow and irregular; the pupil is contracted, and the sight is accommodated for near objects. The respiration is often quick and dyspneic, and râles may be heard over the bronchi, denoting an accumulation of

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mucus in them. Giddiness and confusion of ideas are complained of, but the nervous symptoms are not so conspicuous as those from the peripheral organs. Eventually the respiration becomes slower and great weakness in the movements manifests itself, but consciousness remains more or less perfect until the breathing ceases.

Mushroom Poisoning.—The symptoms of mushroom poisoning are often definitely suggestive of muscarine, *e. g.*, gastro-intestinal irritation, slow pulse and labored respiration. Consciousness may be unaffected, but delirium, convulsions or coma may ensue. Atropine will remove the symptoms due to the peripheral actions of muscarine. Active principles other than muscarine have been described in certain species of mushrooms and the poisonous effects are not invariab y due solely to muscarine. A delayed form of mushroom poisoning is also encountered particularly after the ingestion of *Amanita phalloides* which contain hepatic toxins. Intoxication appears six to fifteen hours after ingesting the mushrooms with violent abdominal pains, nausea, vomiting, etc. Death may occur within about a week from hepatic insufficiency.

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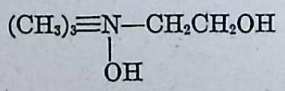
2. Choline, Acetylcholine, and Other Choline Esters

Choline is a constituent of lecithin and is otherwise widely distributed in animal and vegetable tissues. A liter of blood plasma may contain 160 to 300 mg. of choline combined as lecithin. Small amounts of free choline exist in the circulating blood, but the amount occurring in blood or in extracts from tissues after death increases owing to autolysis of lecithin.



Choline

Chemically it may be considered as a derivative of ammonium hydroxide (NH_4OH) in which the four hydrogen atoms attached to the nitrogen are replaced by three methyl and a hydroxyethyl group.

Choline has an important lipotropic function in the organism. Its administration following pancreatectomy, for example, prevents the fatty infiltration of the liver seen in dogs maintained on insulin following this operation. Choline is normally supplied in the diet but can also be synthesized by a combination of methyl groups furnished by methionine with ethanolamine ($NH_2.CH_2.CH_2OH$) which the body can produce. A deficiency of choline in the chick induces perosis and it is

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considered therefore among the substances comprising the vitamin B complex (*cf.* page 601).

The lipotropic action of choline has suggested its therapeutic trial together with methionine in the treatment of cirrhosis of the liver, hepatitis, and other hepatic disorders to avoid the deposition of fat which occurs in this organ in these conditions.

The actions of choline were early found to resemble in many respects those of muscarine, to which it is chemically related. Thus it causes cardiac slowing, increased intestinal movements and increase of lacrimal, salivary and other secretions. In 1908 Reid Hunt described the actions of a number of esters of choline synthetically prepared. He found acetylcholine especially active, having (in respect of its depressor action on the circulation) 100,000 times the activity of choline itself.

In 1914 Dale showed that choline and, with varying degrees of intensification, certain esters and ethers of choline, possess two distinct types of action—a "muscarine" action, paralyzed by atropine, and a "nicotine" action, paralyzed by excess of nicotine. Later Riesser showed that acetylcholine could provoke contracture of the skeletal muscle of amphibia.

These three types of action of acetylcholine have assumed great importance in connection with the chemical transmission of nervous impulses. The outstanding impetus to this conception, which had been earlier foreshadowed, was given by Loewi's demonstration (1921) that the vagus nerve produces its effect on the frog's heart by liberating an inhibitor substance. He showed that this substance (later identified with considerable certainty as acetylcholine), present in the fluid filling the heart, could be transferred to another heart and there reproduce the vagus effect. This conception was extended by many workers, notably by Dale and his collaborators, and the view put forward that acetylcholine may act as a "chemical transmitter" of nervous impulses, not only at the terminations of the postganglionic fibers of the parasympathetic nerves but at the autonomic ganglia and at the terminations of the motor nerves in skeletal muscle. This view offered a new conception of the effect of nerve stimulation, which necessarily also altered our conception of the method of action of many drugs. The action of choline esters, therefore, possesses importance not only for physiology, but for pharmacology, immediate and remote. Here they can be considered merely as pharmacological agents.

Acetylcholine

Acetylcholine, the acetyl derivative of choline, is an unstable substance. It is rapidly hydrolyzed in the presence of alkali to choline and acetate, and has a maximum stability at pH 3.9. In the presence of blood or extracts of most tissues, hydrolysis occurs very rapidly, due to a specific cholinesterase. The amount of this esterase varies widely in blood and different organs of different species, the activity of human blood or serum being very great. Physostigmine has a powerful inhibitory action on cholinesterase and a preliminary injection of physostig-

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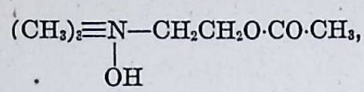
mine enhances the pharmacological effect of most choline esters. Acetylcholine has a double action on the autonomic nervous system, producing effects (*a*) like muscarine and (*b*) like nicotine.



Acetylcholine

"Muscarine"-Action.—These effects are due to a stimulation of the terminations of the postganglionic fibers of the parasympathetic nerves and are, so far as is known, identical with those produced by muscarine. As these effects have already been described under the latter alkaloid, they need only be briefly recapitulated. Acetylcholine causes an increased secretion from the glands innervated by parasympathetic nerves, *e. g.*, salivary, lacrimal, intestinal, as well as of the sweat glands, which are innervated by the sympathetic. It causes a fall of blood-pressure due to dilatation of the vessels, slowing of the heart, and contraction of most forms of involuntary muscle, *e. g.*, of the stomach, intestine, bronchi and uterus. All these effects can be prevented by a small dose of atropine.

"Nicotine"-Action.—These effects are due to a stimulation, followed by paralysis of all the autonomic ganglia of the body, including therefore those connected with the sympathetic as well as those on the course of the parasympathetic nerves. Clearly the result of this action will vary with the dosage. Among the effects under this heading may be mentioned a rise of blood-pressure after atropine. Atropine paralyzes the parasympathetic terminations and prevents both the slowing of the heart and the vasodilatation. Acetylcholine stimulates the parasympathetic and sympathetic ganglia, but atropine prevents the effects of the former. Hence after atropine, acetylcholine stimulates only the sympathetic ganglia and consequently produces a rise of blood-pressure similar to that produced by epinephrine. Large doses of nicotine, by paralyzing these ganglia, prevent the rise of blood-pressure produced under these conditions. The rise may be augmented by an outpouring of epinephrine from the adrenal glands, which are stimulated by acetylcholine.

Another action which acetylcholine shares with nicotine is a stimulant action on voluntary muscles, most readily displayed on the normal muscles of some lower vertebrates and on the motor-denervated muscles of mammals. In the latter, the contraction is slow, but a rapid type of contraction occurs in the normal mammalian muscle (Simonart). This rapid contraction is readily inhibited by curare and is very sensitive to the action of ether and some narcotics. The muscle of the body wall of the leech is stimulated by acetylcholine and this reaction, especially when sensitized by physostigmine, is one of the most delicate biological tests for acetylcholine.

Following the fundamental demonstration by Loewi that stimulation of the vagus nerve to the heart causes the liberation of a substance later

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identified as acetylcholine, the liberation of this substance has been shown to occur in many organs as the result of parasympathetic stimulation, *e. g.*, in the stomach, bladder, lungs and salivary glands. Evidence has also been brought forward to show that there is a liberation of acetylcholine in ganglia when the preganglionic fibers are stimulated and in voluntary muscle when the motor nerves are stimulated.

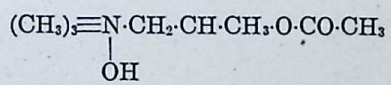
Other Choline Compounds.—Acetylcholine has been more carefully studied than any other ester of choline. Compared with it, propionylcholine has weaker muscarine-actions, but stronger nicotine-actions. With butyrylcholine the muscarine-actions are still feebler but the nicotine-actions remain about the same.

The methyl-, ethyl-, vinyl-, and butyl-, ethers of choline are less active than acetylcholine, especially in respect to nicotine-actions. Acetylhomocholine is much less active than acetylcholine. In the case of muscarine, which can be regarded as choline with an aldehyde group in the α-position and an ethyl group in the β-position, it is possible that the ethyl group is responsible for the absence of nicotine-action, as Simonart has shown that the substitution of a methyl-group in the β-position deprives acetylcholine of its nicotine-action.

Because of its evanescent action in the body, acetylcholine has little therapeutic value and more stable derivatives have therefore been introduced into medical practice to elicit the desired action of this group of compounds.

Acetyl-Beta-Methylcholine (Mecholyl or Mecholine)

Acetyl-beta-methylcholine (mecholyl or mecholine), which is the β-methyl derivative of acetylcholine, resembles acetylcholine quite closely in its effects, but differs from it in being a more stable compound, being less readily hydrolyzed than the acetyl compound. It can be administered by oral as well as by parenteral avenues and is employed also for its local effects induced by means of electrophoresis.



On animals it produces effects similar to those of acetylcholine dependent mainly upon parasympathetic stimulation, as the nicotine-like effects are comparatively feeble. The drug produces changes in the heart characteristic of vagus stimulation, an increase in intestinal peristalsis and tone, constriction of the bronchi and contraction of isolated strips of uterine muscle. There is also salivation and vasodilatation.

In the normal human being doses from 10 to 25 mg. given by subcutaneous injection produce flushing, a feeling of heat, sweating, salivation, lacrimation, increased intestinal peristalsis, discomfort in the epigastrium, palpitation and a feeling of constriction under the sternum. The effects appear in two or three minutes and last for about thirty minutes. With the onset of the symptoms the blood-pressure falls and the heart rate increases. In certain individuals the symptoms appear very rapidly and the blood-pressure fall is so severe that a condition of

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collapse seems imminent necessitating the immediate injection of atropine, which alkaloid quickly removes the effects of the choline compound.

Slowing of the heart may be very marked when the drug is given intravenously and in some cases it has led to complete stoppage so that this method of administration is strongly contraindicated. The point of injection should not be massaged, as such manipulation will hasten absorption and possibly unduly intensify the symptoms. The blood-pressure fall may be rapid and marked, so that the patient should be in the recumbent position when the drug is given in order to prevent fainting. The drug is contraindicated in cases of hyperthyroidism, coronary occlusion, asthma, or in any severe illness. In persons susceptible to asthma it has not infrequently brought on typical attacks.

Therapeutic Uses.—Acetyl-beta-methylcholine may be given orally or by injection. As a palliative in chronic arthritis and in peripheral vascular disorders (*e. g.*, in Raynaud's disease), the method of administration by means of the galvanic current (electrophoresis, iontophoresis, or common ion transfer) is usually much more efficient and the best means of eliciting the local effects of the drug on the extremities.

In this method the direct or galvanic current is used to deposit the ions of certain salts which are in solution either on or in the tissues, where they may be taken up into the blood stream and exert systemic effects. Moreover, when it is desired to get the penetration of the drug into deeper tissues than is possible by simple topical application, the galvanic current has been employed recently and has proved efficient as a mode of administration of acetyl-beta-methylcholine in the treatment of certain vasospastic conditions of the extremities, in chronic ulcers, and as a palliative in rheumatoid arthritis.

To utilize the galvanic current in these conditions the active electrode is saturated with a 0.5 to 2 per cent solution of the acetyl-beta-methylcholine and applied to the part to be treated. This is then wrapped (if an extremity or a joint) with a narrow strip of metal foil arranged to convey the current uniformly to the whole surface to be treated. This foil is connected to the positive pole of the electrical appliance while the negative pole is applied to the patient's back by means of a large dispersive electrode in order to complete the circuit. The strength of the current and the time of its flow will regulate the effectiveness of the ionization. Usually a strength of 40 to 50 milliamperes applied for perhaps twenty minutes is most satisfactory.

This method of application of acetyl-β-methylcholine (and also of histamine) has been shown to produce local effects, such as vasodilation, which are not obtainable by the use of the drug orally or by injection. Also, while at times general systemic symptoms are obtained when this method is employed, these symptoms are less serious than when it is given by injection. Iontophoresis should be employed only by those specially trained in its application. It should not be used directly over ulcers or open wounds and should be used cautiously over scar tissues.

Acetyl-β-methylcholine has been used to some extent to elicit its effects on the gastro-intestinal tract (*e. g.*, in ileus), and on the urinary

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bladder but is less suitable for these purposes than neostigmin and carbaminoylcholine respectively.

Acetyl-β-methylcholine (mecholyl) is used in the form of its water-soluble salts. The chloride is very hygroscopic and is therefore not suitable for oral administration in crystal form but should be given in solution.

Mecholyl chloride is injected subcutaneously in the treatment of selected cases of paroxysmal auricular tachycardia which have not responded to the other usual therapeutic measures. A dose of 10 mg. is used on the first injection and only if well tolerated may this be cautiously increased up to 20 to 40 mg. It is advisable to wait about ten to twenty minutes before repeating an injection and to first massage gently at the site of the first injection to ensure that its effect has disappeared. Overdosage effects may be abolished by an injection of 0.6 mg. atropine sulfate.

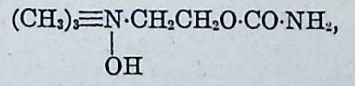
The therapeutically effective oral dose of mecholyl chloride ranges from 0.2 to 0.5 gram, two or three times a day. Smaller doses (0.05 to 0.1 gram) are effective in overcoming the vascular spasm due to moderate exposure to cold.

Mecholyl bromide is less hygroscopic than the chloride and is suitable for use in tablet form. It is used only orally, the chloride being preferred for iontophoresis. The bromide is administered in doses of 0.2 to 0.6 gram (1 to 3 tablets) two or three times daily. If a total daily dose of 2 grams is ineffective, its use should be abandoned in favor of the chloride administered subcutaneously, by local application, or by iontophoresis.

Mecholyl may be used as a diagnostic and prognostic test in cases of suspected poisoning by the atropine series of drugs (Dameshek and Feinsilver). In the presence of a very small amount of the drugs of the atropine series, mecholyl fails to cause its characteristic effects.

Carbaminoylcholine (Carbachol)

Carbaminoylcholine differs from acetylcholine in having an NH_2 group instead of CH_3. It was introduced into therapeutics in 1932 under the trade-names, doryl and lentin, as a substitute for acetylcholine.



$$(CH_3)_3\equiv\underset{\underset{OH}{|}}{N}\cdot CH_2CH_2O\cdot CO\cdot NH_2,$$

Carbaminoylcholine has an activity on the blood-pressure about equal to that of acetylcholine but it is much more stable and is effective when given by mouth. Administered to man intravenously in doses of 0.25 to 0.5 mg., carbaminoylcholine causes a rapid fall in both systolic and diastolic blood-pressure with a marked rise in pulse rate. These changes reach their maximum in about thirty seconds and then pass off equally rapidly. They may be accompanied by flushing of the head and neck and a feeling of heat throughout the body and a sensation of constriction in the throat and chest. These symptoms also pass off quickly.

When the drug is given by intramuscular injection, the symptoms

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are much the same as those described, except that their onset is slower and their duration more prolonged. The flushing and feeling of heat may be accompanied by salivation, lacrimation, sweating, a feeling of constriction in the throat, nausea, and a feeling of unrest in the abdomen. These symptoms, like the circulatory changes, usually pass off in about one-half hour. In some cases, they are quite severe and may lead to collapse. In such cases, prompt recovery follows an injection of atropine.

Carbaminoylcholine in the form of its hydrochloride has been used in the form of 0.2 and 0.4 mg. tablets for oral use and for hypodermic injection as well as in solution for application to mucous membranes. The drug has a more pronounced action on the gastro-intestinal tract and urinary bladder and lesser effect upon the heart, as compared to acetyl-β-methylcholine.

In the eye in glaucoma, dilute solutions (0.75 per cent) instilled into the conjunctival sac will cause a marked constriction of the iris and lowering of the intra-ocular pressure. For this purpose it may be combined with a very small amount of physostigmine, the latter drug intensifying and prolonging the action.

In general, the action of this compound in man is much the same as that of acetylcholine itself, except that the action is more prolonged and can be induced by intramuscular and subcutaneous administration as well as by the oral route, although the latter method is less reliable.

Carbaminoylcholine has found its principal clinical application in the treatment of urinary retention. The effective dose is 0.25 mg. injected subcutaneously. However, great care must be exercised in the use of the drug since untoward reactions are frequent. These are not readily counteracted by the usual therapeutic dose of atropine (0.6 mg.).

Carbaminoycholine or carbachol is official in the British Pharmacopoeia under the title Carbacholum.

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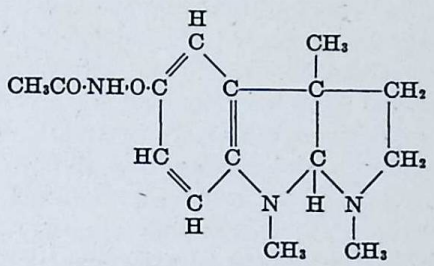
3. Physostigmine and Neostigmine

Physostigmine or Eserine is the chief alkaloid of the Calabar bean, or Ordeal bean (Physostigma venenosum), which grows in Western Africa and was employed there by the natives in the trials by ordeal for witchcraft. Either physostigmine itself, or a nearly allied alkaloid, occurs also in the Kali or Cali nuts, the seeds of *Mucuna urens*. The constitution of physostigmine ($C_{15}H_{21}N_3O_2$) is given below.



It has been prepared synthetically (Julian and Pike).

The actions of physostigmine were first examined in detail by Fraser who described (1863–1868) the constriction of the pupil, slowing of the heart, and increase of glandular secretions produced by this alkaloid. Later it was classed with muscarine in that its effects could be partly explained by its stimulating parasympathetic nerve-ends. Hunt (1918) found that it had a sensitizing effect on the actions of acetylcholine and later Loewi showed that minute amounts of physostigmine inhibited the activity of the specific esterase which inactivates acetylcholine. The peripheral actions of physostigmine are therefore partly indirect, due to its prolonging the action of acetylcholine liberated at the nerve-ends and probably partly to a direct action of the alkaloid itself. (See page 445.)

A number of other alkaloids have been stated to occur in Calabar bean, but their existence is not sufficiently established in most cases and little is known of their action. They have been named *Calabarine, Isophysostigmine, Geneserine, Eseridine,* etc. According to Heathcote, eseridine possesses about one-tenth of the activity of physostigmine and acts similarly.

Symptoms.—The symptoms of poisoning vary but little in different animals; in the dog and rabbit the first results of a large dose of physostigmine are weakness in the voluntary movements and a curious tremor and muscular twitching, beginning in the hind legs, but soon extending over the whole body. The animal falls on one side and cannot raise itself again, although it makes efforts to do so when touched. The saliva and tears are increased, the bowel is often evacuated and in the

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dog vomiting is common. The respiration is at first rapid and deep, and later slow and dyspneic, the heart is weak and slow, and the pupil is contracted to a small point. These symptoms become more marked as more of the poison reaches the blood, until the respiration ceases. In cats these symptoms of depression and paralysis are preceded by a stage of increased movement and evident anxiety, but the later symptoms resemble those in the dog. In man physostigmine elicits practically the same results as in the dog, vomiting and pain in the stomach region, dyspnea, giddiness and muscular weakness, contraction of the pupil, salivation, and perspiration. The heart is slow, muscular twitching may be present, and complete collapse follows. In frogs the voluntary movements disappear soon after the injection of physostigmine, the respiration ceases, and last of all the reflexes are paralyzed.

Central Nervous System.—In cases of poisoning in man, the consciousness is preserved until late, which indicates that the highest functions of the brain are not directly affected by physostigmine. The motor cerebral cortex is apparently rendered more excitable, for in epileptics the number and intensity of the seizures increase under its use, and in guinea-pigs rendered epileptic by operative procedures the same aggravation is seen after it. In the dog epileptiform convulsions occur occasionally, while in the cat a stage of excitement is generally present, and irregular muscular movements, such as nystagmus, are seen in these and other animals. It is possible, however, that some of these effects may arise from the peripheral action of the poison, for example from the partial asphyxia from broncho-constriction; they all disappear after the injection of atropine. The depression and muscular weakness which are seen in animals under large doses probably arise from affection of lower parts of the central nervous system and resemble the condition known as collapse more than that of narcosis.

Quite apart from these central effects, physostigmine causes twitching of the voluntary muscles which is not prevented by division of the nerves and is therefore peripheral in origin; this symptom is not marked in the frog, but may be so developed in mammals as to simulate convulsions. It is arrested by curare, but not by atropine. Curare and physostigmine are mutual antagonists, for the paralysis of curare may be removed by physostigmine and on the other hand the twitching induced by physostigmine is arrested by curare; and this suggests that they act at the same point. Acetylcholine produces a similar effect on muscle which is accentuated by physostigmine. It is probable, therefore, that the fibrillary twitches produced by physostigmine are really due to acetylcholine (Simonart).

Physostigmine has also been shown to remove the paralyzing effect of nicotine and curare upon the ganglia of both sympathetic and parasympathetic systems. Soon after the stimulation of the peripheral ends of the vagus or of the cervical sympathetic nerves has ceased to have an effect due to the paralyzing action of either of the two drugs, the nerves will once more display normal activity if a small dose of physostigmine is injected. This action of the physostigmine is due to its removal of the block produced by the curare or nicotine to the acetylcholine transmission of the nerve impulse through the synapses, either by lowering the threshold of the ganglionic cells to acetylcholine or by increasing

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the amount of acetylcholine available by preventing its destruction by the choline esterase.

There is also a mutual antagonistic action between atropine and physostigmine as relatively small doses of atropine will protect the animal against the action of physostigmine on the secretory system, on the smooth muscle, and also prevent the clonic convulsions characteristic of toxic doses of the drug. It does not prevent the muscular fibrillation of physostigmine, and its antagonism against the effect on the respiration is incomplete.

The **Respiration** is at first somewhat accelerated and then becomes slow and weak. The preliminary acceleration may arise from central stimulation, or possibly from partial asphyxia due to constriction of the bronchi. The subsequent weakness and slowness of the breathing is undoubtedly of central origin, and death follows from the failure of the respiratory center.

The changes in the **Circulation** require further investigation. Small doses slow the pulse and increase the blood-pressure, while larger doses are followed by greater slowing of the heart and a fall in the blood-pressure. In the dog the slowing of the heart is due to stimulation of the vagal terminations and is prevented by atropine, but in the rabbit and frog this does not occur (Heathcote). According to several observers, the irritability of the terminations of the inhibitory fibers in the heart is increased, so that stimulation of the vagus is more effective after physostigmine—an observation that readily falls into line with the view that vagus stimulation causes an output of acetylcholine and that physostigmine augments this action by inhibiting the effect of cholinesterase.

The increased blood-pressure has also been the subject of some discussion. It seems independent, in part at least, of the vasomotor center, for it is not prevented by section of the spinal cord or of the splanchnic nerves, operations which prevent impulses from the center reaching the vessels. It may be partly due to the powerful contraction of the intestines expelling the blood from the mesenteric area, or to a stimulation of the vasomotor ganglia.

The frog's heart beats more slowly after physostigmine, but here the individual contractions are said to be strengthened and prolonged, and there is definite evidence of stimulation of the heart muscle, which is not seen in mammals. If the vagus be stimulated in the frog after physostigmine, it produces slowing but no complete standstill of the heart, because the irritability of the muscle is so much augmented that the inhibitory apparatus can no longer entirely control it. If such a poison as muscarine produces complete standstill, physostigmine removes it, not by depressing the inhibitory apparatus, but by increasing the irritability of the muscle.

The **Secretions** are increased by physostigmine as by pilocarpine and muscarine; thus the *saliva*, the *tears*, the *perspiration*, the *mucus* secretion and the *pancreatic juice* are all augmented.

Muscle.—Physostigmine produces powerful contractions of the *Stomach, Intestine, Uterus, Ureter, Bladder, Spleen* and *Bronchial Muscle* resembling those elicited by muscarine and pilocarpine.

The *Intra-ocular Muscles* also undergo contraction, and their movements under physostigmine have been the subject of a large number of

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investigations and of a good deal of controversy. The pupil contracts when physostigmine is employed either locally or internally, and this contraction may be lessened by the subsequent application of atropine, but is not altogether removed except by large quantities. On the other hand, the dilatation of the pupil produced by small quantities of atropine may be diminished by physostigmine, but the resulting contraction is much less than that caused by physostigmine applied to the normal eye. The ciliary muscle is acted on in the same way as the iris, so that the eye becomes accommodated for near distance, and atropine induces the same modifications. After removal of the ciliary ganglion, physostigmine and neostigmine no longer constrict the pupil (Anderson). This is to be anticipated if one assumes that these drugs do not stimulate directly the muscle of the iris but only act through their effects in inactivating cholinesterase with the consequent preservation of the stimulant quantities of acetylcholine. The last named substance will obviously only be present when the ganglion cells are intact or the postganglionic fibers are stimulated (Leopold and Comroe). The intra-ocular pressure is reduced by the application of physostigmine to the eye and this has generally been attributed to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana. Another factor may be contraction of the intra-ocular vessels, which lessens the secretion.

The effects of physostigmine, then, on the secretory organs, pupil and ciliary muscle are strictly analogous, and are generally attributed to the alkaloid stimulating the terminations of the nerves in these organs. The antagonism of physostigmine to atropine is more complete than that of pilocarpine, for a renewal of the contraction can be elicited more easily by the former alkaloid. In the *stomach* physostigmine produces an increase in tone in from three to ten minutes, the organ becoming smaller and the outline sharper. This increased tone may last for an hour. The peristaltic waves are deep and powerful and force the gastric contents through the pylorus more rapidly than normal. These effects of physostigmine on the stomach may be of value when roentgenological examinations of the organ are being made.

Peripheral Action.—It has been discussed whether physostigmine actually stimulates the myoneural junctions, that is, causes impulses to be emitted by them as pilocarpine does, or whether it merely renders them more sensitive to stimuli descending the nerve fibers; the latter seems to be the case in some instances, for it is found that when the chorda tympani nerve is cut physostigmine often fails to cause secretion, though electrical stimulation of the nerve is more efficient than before. In other instances physostigmine appears to act after the impulses from above are excluded, so that here it has the same action as pilocarpine. It is possible that the failure of physostigmine to contract the pupil after degeneration of the postganglionic ciliary branches may be due to the exclusion of the impulses from the centers (Loewi and Mansfeld). Another explanation of the action of physostigmine is provided by Loewi, which relates it to the humoral transmission of parasympathetic impulses (v. Acetylcholine, page 445). He found that

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acetylcholine is readily destroyed by an esterase in the blood and tissues and that physostigmine has a specific effect in preventing this destruction. This would explain its failure to act on denervated organs in which no acetylcholine is liberated. Stedman has found that, of a series of compounds related to physostigmine, those which exhibited miotic activity also possessed the property of inhibiting the activity of esterases. This supports the probability that the actions of physostigmine are due to its inhibiting the activity of cholinesterase. Whether this effect on esterases accounts for the entire pharmacological activity of physostigmine or whether the alkaloid has an additional direct action has been recently investigated by Manning, Lang and Hall who have shown that amounts of physostigmine which are too small to produce demonstrable pharmacological effects will yet be sufficient to inhibit the cholinesterase and at the same time enhance parasympathetic excitability.

The alkaloid itself does not elicit its own specific pharmacological response until a sufficient dose is given to exceed the quantity necessary to inhibit the esterase to a maximal degree.

The effect of the inhibition of the cholinesterase is to prevent the rapid destruction of acetylcholine with resulting exaggeration of the effects of vagus stimulation or of amounts of acetylcholine which might be injected. When the saturation point of the enzyme system by physostigmine is reached, inhibition is maximal and now additional amounts of the alkaloid will produce parasympathetic effects.

The action of physostigmine is further complicated by its increasing the amount of epinephrine secreted into the blood. This may act in the same direction as physostigmine, for example, on the motor fibers of the uterus, or may oppose it, for example, by inhibiting the movements of the intestine which physostigmine augments; in some conditions the injection of physostigmine may actually arrest peristalsis from this secondary effect.

Physostigmine increases the blood sugar of rats, the maximum increase being in one hour with return to normal in two hours. This action is prevented by the previous administration of atropine.

Physostigmine and strychnine are said to act synergistically in the production of hyperglycemia in rats, the combination of both drugs producing a greater increase in blood sugar than the sum of effects of each given separately.

Some physostigmine is **Excreted** in the urine, but most of that ingested is destroyed in the tissues. It has also been found in the saliva and bile.

The symptoms of poisoning with Calabar bean are identical with those caused by physostigmine, except when an old preparation is used, when some stimulation of the spinal cord may be induced.

Therapeutic Uses.—Physostigmine is used chiefly for its action on the intra-ocular muscles and tension. For this purpose a solution of $\frac{1}{3}$ to 1 per cent is dropped in the eye, 2 to 4 drops at a time, or small discs of gelatin impregnated with the alkaloid may be applied to the conjunctiva (B. P.). The pupil begins to contract in five to fifteen minutes, and attains its smallest size in half an hour. It remains contracted twelve to fourteen hours; according to some observers a difference in

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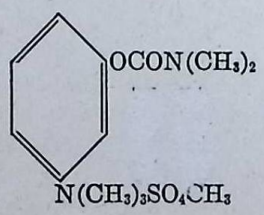
the size of the two pupils may be made out for several days. The ciliary muscle contracts along with the iris, and vision becomes accommodated for short distances. This action on the accommodation passes off in two to four hours, but the sight is often rendered indistinct for some hours. The action of physostigmine on the eye differs from that of muscarine, for the former acts more on the pupil, the latter on the ciliary muscle, and the pupil is often contracted by physostigmine while the accommodation is practically unchanged. The intra-ocular pressure is somewhat increased at first but subsequently sinks. Its action in narrowing the pupil after atropine has been made use of to remove the dilatation produced so frequently in ophthalmological practice. It antagonizes the dilatation of the pupil after homatropine and cocaine much more successfully than that due to atropine. Physostigmine is extensively employed to reduce the intra-ocular pressure in glaucoma.

In 1934, Walker introduced the use of physostigmine for the symptomatic control of myasthenia gravis a condition characterized by easy fatigability and paresis of the voluntary muscles which resembles that which occurs in curare poisoning. She subsequently found that neostigmine exerts a similar effect and has certain advantages over physostigmine which it has replaced in the treatment of myasthenia gravis.

Neostigmine

The fact that the physiological activity of physostigmine disappears on hydrolysis suggested to Stedman that its activity was due to the urethan grouping (*cf.* formula, page 451). He prepared a number of substances containing this group and found that these also possess a miotic action similar to that of physostigmine. In general, all compounds of the general formula $RNHCOOC_6H_4R'$, where R is a methyl or ethyl group and R′ a basic substituent such as $-N(CH_3)_2$ are active. The activity is greatest when R is a methyl group, as occurs in physostigmine itself. Aeschlimann and Reinert investigated a further series of such compounds and showed that one of these (the dimethyl-carbamic ester of 3-hydroxyphenyl-trimethylammonium-methylsulfate) was as active as physostigmine in stimulating intestinal peristalsis but had less effect on the heart and circulation. This compound which has the following formula:



was introduced into medicine under the trade-name, "*Prostigmin,*" and has been extensively used as a substitute for physostigmine in the treatment of intestinal atony and of myasthenia gravis with successful results. It is officially designated as Neostigmine.

Neostigmine has the advantage over physostigmine of being more

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stable. When used in toxic doses, it produces symptoms similar to those of physostigmine. These symptoms are counteracted by atropine.

Neostigmine is available in the form of its salt, neostigmine bromide, which is used in the treatment of myasthenia gravis. One 15 mg. tablet is administered three times daily but if necessary this dose may be cautiously increased to 30 mg. three times daily. For parenteral administration, neostigmine methylsulfate which is available in 1 cc. ampules of a 1:2000 and 1:4000 solution, is used. These solutions are administered subcutaneously or intramuscularly in doses of 1 cc. for the relief of abdominal distention for the prevention of atony of the intestinal and bladder musculature, and for the symptomatic treatment of myasthenia gravis. The use of neostigmine has also been advocated in poliomyelitis to relieve muscular spasm and aid in the re-establishment of muscle coordination.

On the human stomach Veach, Laner and James found that neostigmine exerted an inhibitory action and that atropine following it produced a motor effect. However, if atropine were given first exerting its usual inhibitory action, a subsequent injection of neostigmine had a stimulating effect. Neostigmine is constantly motor to the colon and this action is removed by atropine.

Neostigmine exerts a definite synergistic action on the effects of mecholyl (acetyl-beta-methyl-choline chloride) on the sweat glands, flushing, gastric secretion and cardiovascular system in man. For instance, neostigmine itself produces no sweating, flushing or lacrimation, and mecholyl produces these effects only to a minor degree but if mecholyl is given a few minutes after a small dose of neostigmine, it is followed by a very marked reaction. This reaction may take the form of local sweating, or in case of the gastric secretion, the acid content drops very suddenly and the quantity of gastric juice increases greatly.

In the cardiovascular system the synergistic action is equally well marked. Doses of 5 mg. of mecholyl may cause a slight increase in heart rate and blood-pressure; rarely a fall in pressure. If the mecholyl is given a few minutes after 0.5 mg. of neostigmine, the reaction is usually very pronounced, even leading to collapse. There is a very pronounced fall in blood-pressure together with an increase in pulse rate followed by a marked fall. With larger doses of mecholyl following the neostigmine, the cardiac changes are more severe—with sinus bradycardia and partial or total heart block. These effects can be prevented or removed by the use of atropine.

Certain substances which are related to physostigmine other than neostigmine have also an anticurare action. Perhaps the best known is the methylphenyl carbamic ester of 3-oxyphenyl trimethyl ammonium methyl sulfate (substance 36). This compound has been shown to act antagonistically to curare and like neostigmine it has been used successfully in myasthenia gravis.

Guanidine, $NHC(NH_2)_2$, and methylguanidine, $NHCNH_2NHCH_3$, two bases occurring in animals and plants, resemble physostigmine in their effects, causing fibrillary twitching of the muscles, which is opposed by curare and obviously arises from stimulation of the same myoneural receptors as are affected by physostigmine. Vomiting, salivation, bronchial spasm also occur as under physostigmine. On the other hand, the central nervous system is more distinctly stimulated, for violent convulsions are induced by guanidine, these arising partly from the brain and partly from the cord.

Synthalin, the decamethylene derivative of diguanidine, $(CH_2)_{10}(NH_2.NH:C.NH)_2$, is less toxic than guanidine but shows a more pronounced hypoglycemic effect. This results from its toxic effects on the liver. The use of this or related compounds in diabetes is irrational and harmful. Extracts of certain plants exert a similar hypoglycemic effect and are the basis for quack remedies for diabetes.

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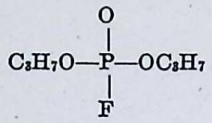
Di-isopropyl Fluorophosphate

Di-isopropyl fluorophosphate **(DFP)** is the di-isopropyl ester of fluorophosphoric acid with the structure shown in the accompanying formula. It was developed during the recent war as a possible weapon for inducing paralysis of the nerves. The fluorophosphates as a group inhibit cholinesterase, this action being enhanced when alkyl groups are substituted for the hydrogen which also renders the compounds highly lipid soluble.



Di-isopropyl fluorophosphate (DFP) is not only highly active as an anti-cholinesterase but the inhibition of cholinesterase activity is irreversible. Hence only by the synthesis of new enzyme can the ability of the tissues to hydrolyze acetylcholine be restored. By injecting DFP it is possible to completely inhibit the cholinesterase of the serum without affecting significantly that present in other tissues. The compound has been used experimentally in an attempt to elucidate the role of acetylcholine in the transmission of the nerve impulse. It has been demonstrated, for example, that no disturbance in conduction of the isolated sciatic nerve of the frog follows complete destruction of cholinesterase, a finding which is incompatible with the view that acetylcholine plays a role in axonal conduction.

DFP has been tried experimentally as a possible therapeutic agent in the treatment of myasthenia gravis, glaucoma and other conditions in which inhibition of cholinesterase is desirable. Undesirable side effects especially on the gastro-intestinal tract preclude its use in maximally effective doses in myasthenia gravis. In glaucoma, on the other hand, it has proven superior to other miotics in reducing intraocular pressure, in some patients.

Preparations

Physostigminæ Salicylas, eserine salicylate. Dose (U. S. P.), 2 mg.; B. P., 0.0006 to 0.0012 gram.

Lamellæ Physostigminæ (B. P.), each containing 0.065 mg. of physostigmine salicylate.

The salicylate of physostigmine forms colorless or faintly yellow crystals, without odor, but possessing a bitter taste. The salicylate has usually a slight acid reaction, and is soluble in about 100 parts of cold, or 30 parts of boiling water. It undergoes decomposition when kept in solution and then assumes a reddish-brown color; the addition of boric or sulfurous acid to the solution is said to retard this decomposition.

Neostigminæ Bromidum (U. S. P.), a white powder, soluble in water. Dose, 15 mg. orally.

Tabellæ Neostigminæ Bromidi (U. S. P.). Dose, 15 mg.

Neostigminæ Methylsulfas (U. S. P.). Dose, 0.5 mg., subcutaneously.

Injectio Neostigminæ Methylsulfatis (U. S. P.). Dose, 0.5 mg., subcutaneously.

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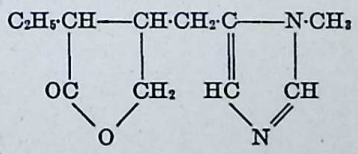
4. Pilocarpine

Pilocarpine is an alkaloid found with Isopilocarpine in the leaves of several species of Pilocarpus. It has the following structural formula:



Pilocarpine stimulates the terminations of the postganglionic fibers of the parasympathetic nerves. It therefore acts in the same way as muscarine and the symptoms produced by both are nearly identical. Pilocarpine does not potentiate the actions of acetylcholine as does physostigmine.

Pilocarpine stimulates the secretion of all *glands* innervated by the parasympathetic nerves, *e. g.*, salivary, lacrimal, gastric, intestinal and bronchial glands. The salivary secretion may amount to one-half liter or more in the course of two or three hours after an injection of pilocarpine, while the skin and lungs excrete even a larger quantity of

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fluid in the same time. The weight is thus considerably reduced by pilocarpine, owing to the loss of fluid, which may, according to some authors, amount to 2 to 4 kilograms after a single dose. The increased activity of the glands is accompanied by an acceleration of the blood current through them. This may be partly due to the increased activity of the glands, though pilocarpine may also have a direct dilator effect on the vessels supplying them.

Pilocarpine produces a profuse secretion from the bronchial glands. Large doses may produce dangerous pulmonary edema from aspiration of fluid as well as from the depression of the circulation.

The sweat glands, though innervated by the sympathetic, are also stimulated by pilocarpine. In man it is found that, in cases of complete interruption of the nervous paths in the cord, small doses of pilocarpine cause no sweating in the lower part of the body. This does not seem due to the division of the secretory fibers proper, for division of the sympathetic nerves alone does not impair the sweating under pilocarpine; more probably the failure of pilocarpine to cause sweating in these cases arises from the disturbance of the circulation through the break in the afferent and vasodilator path (Burn). All those effects on glands are prevented by atropine, as is shown for the gastric secretion in Fig. 34.

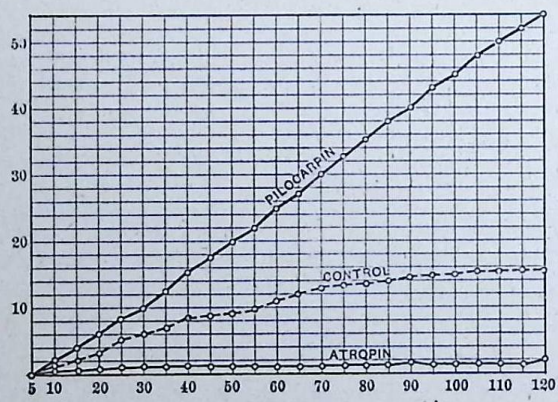

FIG. 34.—Chart of the gastric secretion in the dog under pilocarpine and atropine. Three observations were made: in one milk alone was given, in another milk with pilocarpine, and in a third milk with atropine. The amount of secretion was noted in a small isolated pouch of the stomach, and is indicated graphically in the chart. (Riegel)

Salivary glands which have had the chorda tympani cut respond to the injection of pilocarpine more promptly and more vigorously than do the normal intact glands. This increased response which appears in two or three weeks after cutting the nerve was found to exist undiminished for a year afterwards. No explanation can be given for this increased response to the drug.

Pilocarpine also stimulates the parasympathetic effector cells in involuntary muscle, *e. g.*, of the alimentary canal, bronchi, spleen, bladder, ureters, etc. Repeated evacuations of the intestines may occur from stimulation of both muscle and glands. There may be frequent emptying of the bladder with straining. Retching and vomiting occur less

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often with pilocarpine than with muscarine. Pilocarpine causes contraction of the pupil, and of the ciliary muscle, with a lowering of intra-ocular pressure. The pupil of the rat is exceptional in being dilated by pilocarpine. Pilocarpine has no effect on the pupil in birds, in which the muscle of the iris is striated.

The effects produced by pilocarpine on the **circulation** are somewhat variable according to the species as well as the dose administered. They differ in some respects from those produced by muscarine. Like muscarine, pilocarpine locally applied causes slowing or actual diastolic standstill of the heart from stimulation of the vagus endings, an effect prevented by atropine. When injected intravenously pilocarpine produces, in rabbits and cats a fall of blood-pressure due to slowing of the heart and dilatation of the arterioles. Pilocarpine differs from muscarine here in several particulars, for it soon depresses the inhibitory fibers and the heart regains its former rhythm, but the cardiac muscle is then affected, so that the contractions rapidly become weaker and slower again, and this secondary slowing is not removed by atropine; the vasomotor center also becomes gradually weakened by large doses, so that the blood-vessels remain somewhat dilated, and the arterial tension remains low even after atropine. In the decapitate (but not in the decerebrate nor in the anesthetized) cat, the fall of blood-pressure which follows on the injection of pilocarpine, is succeeded by a secondary rise of considerable height and duration. This may be due to a stimulant action on the preganglionic sympathetic fibers (Heaton and MacKeith), which may explain some of the anomalous effects on the circulation produced by pilocarpine. In dogs and in man, the stimulation of the inhibitory fibers seems sometimes to be absent, and acceleration of the pulse occurs, accompanied by palpitation, with a rise of blood-pressure.

Pilocarpine increases the **Leucocytes** of the blood, which are pressed out of the spleen by the contractions of the smooth muscle.

Administered to normal rats pilocarpine causes a marked increase in **blood sugar**, the maximum effect being attained in fifteen minutes with return to the normal level in one hour. These changes in blood sugar are prevented by the administration of atropine.

Some symptoms occur in cases of poisoning which point to some action of the alkaloid on the **Central Nervous System.** Thus frogs develop well-marked convulsions, and even in the higher animals and man tremor and slight convulsive movements, such as hiccough, have been observed. The collapse which is seen in the later stages may be central in origin but probably is largely the result of the peripheral action, and the convulsions, which occur in some cases, arise from anemia of the brain as the result of the cardiac weakness.

Therapeutic Uses of Pilocarpine.—Its action on the sweat glands renders pilocarpine much the most powerful sudorific in the pharmacopeia, but it is used only rarely now for this purpose. Its principal use therapeutically is as a miotic in ophthalmology to contract the pupil and reduce the intra-ocular pressure, particularly in glaucoma. A 1 to 2 per cent solution of the hydrochloride or a 2 per cent solution of the nitrate are employed for this purpose. The drug may also be applied to the

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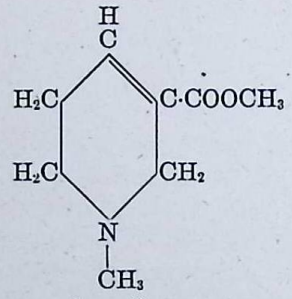
conjunctiva in the form of an ointment or in gelatin lamellæ containing $\frac{1}{4}$ mg. of the drug.

The contraction of the pupil generally attains its maximum in about one-half to one hour, and passes off in three to five hours; it is less complete and of shorter duration than that seen after physostigmine. Pilocarpine is said to first increase and then lower the intra-ocular tension.

Pilocarpine has also been advocated to relieve the itching which accompanies liver disorders, in labyrinthine disease of the middle ear, in xerostomia, and as an expectorant.

In cases of atropine poisoning, the use of pilocarpine is quite unjustified as the danger arises from the central nervous system in which the action of atropine is not antagonized by pilocarpine. In poisoning from pilocarpine or muscarine small quantities of atropine are the antidote recommended alike by pharmacological experiment and by clinical experience.

Poisoning due to pilocarpine is rare, the symptoms resembling those of muscarine intoxication.



Arecoline

Arecoline, one of the alkaloids in Betel nuts (*Areca Catechu*) resembles pilocarpine in its actions although quite unlike it in chemical structure. Like pilocarpine, it stimulates smooth muscles and gland cells innervated by postganglionic cholinergic nerve fibers, but is more powerful in its action.

Preparations

Pilocarpinæ Nitras (U. S. P., B. P.) ($C_{11}H_{16}N_2O_2.HNO_3$), the nitrate of an alkaloid obtained from Pilocarpus leaves, forms a white crystalline powder, which is soluble in about 8 parts of cold water. Dose, 0.005 gram; B. P., 0.003 to 0.012 gram.

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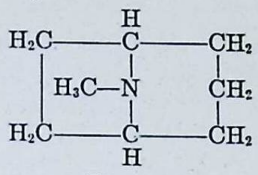
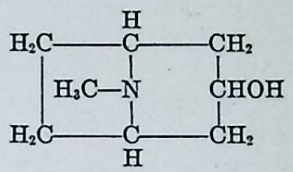
III. SUBSTANCES DEPRESSING PARASYMPATHETIC ACTIVITY

1. The Atropine Series

The atropine series contains a number of very closely allied alkaloids of which the chief are *Atropine*, *Hyoscyamine* and *Hyoscine* or *Scopolamine*. They are found in the roots and leaves of many plants of the Solanaceæ order, notably belladonna (*Atropa belladonna*), henbane (*Hyoscyamus niger*) and the thorn apple or jimson weed (*Datura stramonium*).



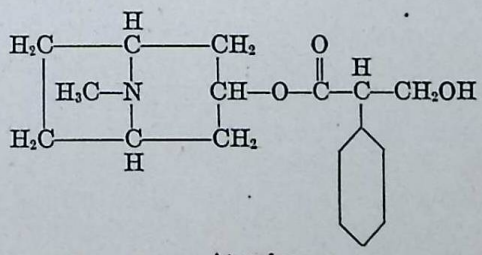
Tropane



Tropine

Chemistry.—The alkaloids of this group are derived from a combination of a piperidine and a pyrrolidine ring, designated as tropane. The 3-hydroxy derivative of tropane is known as tropine and is the basic component of atropine. When atropine is hydrolyzed, it forms tropine and tropic acid. The latter is α-phenyl-β-hydroxypropionic acid. Atropine as shown in the accompanying formula is the tropic acid ester of tropine. It has been prepared synthetically. Tropic acid contains an asymmetric carbon atom. The racemic compound (atropine) as obtained naturally or as synthesized is resolved into its optically active components, *d*- and *l*-hyoscyamine. Atropine is racemic hyoscyamine, that is, it consists of equal parts of levo-hyoscyamine and dextro-hyoscyamine, but, as the latter is only feebly active in the body, the action of atropine is practically that of its levo-hyoscyamine half. Levo-hyoscyamine is formed in the plants, but is readily changed to atropine in the plant cells and also in the process of extraction, so that the relative proportion of the isomers in the plants and in the preparations varies. However, atropine itself does exist in small amount as such in the plants although most of it is formed from the *l*-hyoscyamine in the process of extraction.

Hyoscine or *Scopolamine* ($C_{17}H_{21}NO_4$) is very closely allied to atropine, and is decomposed by very mild hydrolysis into its components—tropic acid and scopine.



Atropine

Scopolamine is levorotatory, but is readily racemized to the *d*, *l*-form known as *atroscine*. When hydrolyzed in the usual way, scopolamine

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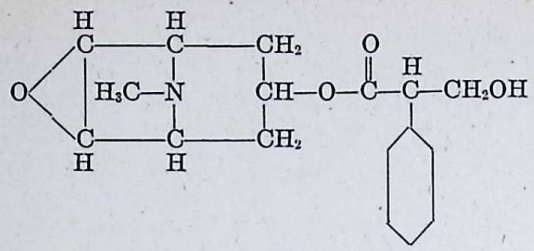
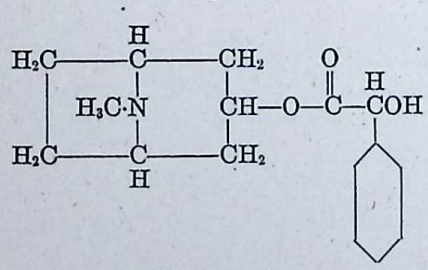
forms tropic acid and scopoline (oscine), a compound into which scopine also readily passes by molecular rearrangement.



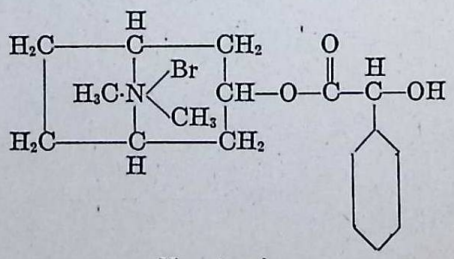
Scopolamine (hyoscine)

A number of related compounds are also present in the Solanaceous plants and in some Duboisia and Scopolia species. Apoatropine (atropamine) which is found in belladonna root may also be prepared synthetically by dehydrating atropine. It is an ester of tropine and atropic acid (α-phenylacrylic acid). Belladonnine, an isomer of apoatropine, also is present in belladonna root. Norhyoscyamine (pseudohyoscyamine) present in *Duboisia, Scopolia* and *Datura* consists of tropic acid and Nortropine, a tropine containing an NH group in place of NCH_3.

After atropine had been found to be a compound of tropine and tropic acid, a number of other acids were attached to tropine in the same way as tropic acid. These artificial alkaloids are known as *Tropeines,* and in action resemble atropine in some points while differing from it in others. Several artificial tropeines have been introduced in medicine, the most important of which is the ester of tropine and mandelic acid known as *Homatropine.*



Homatropine



Novatropine

The methylbromide of homatropine, novatropine, and the corresponding methyl nitrate derivative, eumydrine, are also used in therapeutics. Other synthetic compounds (eucatropine, syntropan, trasentin) intro-

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duced as substitutes for atropine consist of esters of tertiary amino bases and are only remotely related to atropine chemically.

These alkaloids all resemble each other closely in the effects produced by them in animals. Some differences in the symptoms exist, however, and the action of atropine alone will first be described and later the points in which that of hyoscyamine and of scopolamine differ from it.

Atropine acts as a stimulant, and in toxic doses as a depressant, to the central nervous system. It also affects a number of organs, especially those containing smooth muscle or secreting glands, producing its effects largely by paralyzing the terminations of the parasympathetic nerves.

Symptoms.—In man, 0.6 mg. causes some dryness of the mouth and throat, and thirst; the skin also feels dry, and the heart may be accelerated after a short period of slowing. Doses of 2.5 mg. are followed by marked dryness of the skin and throat, thirst, difficulty in swallowing and hoarseness in speaking. There is often nausea, and in some cases vomiting, headache, and giddiness; the pupils are wider than normal and the sight may be indistinct, especially for near objects. The respiration may be quicker and the pulse often beats at one hundred per minute or more. A symptom that is often present, though by no means invariably so, is redness of the skin, especially of the head and neck; the conjunctiva may also be congested. After larger doses the same symptoms are observed, but are soon followed by others of graver import. The patient can no longer swallow, although suffering from intense thirst, the heart is generally extremely rapid, speech is difficult and hoarse, and the pupils are dilated until the iris almost disappears. Restlessness and garrulity point to an increase in the irritability of the brain; the patient at first talks in a perfectly normal way but soon becomes confused, begins a sentence and does not finish it, often bursts into laughter or sobs, and in short becomes delirious and eventually maniacal. Often marked tremor of different muscles may be observed, and eventually convulsions set in and may be the cause of death through the failure of the respiration. As a general rule, however, the stage of excitement passes into one of depression, the patient sinks into a sleep, which deepens into stupor and coma, the respiration and heart become slow, weak and irregular, and death eventually occurs from asphyxia.

In the frog the injection of small quantities of atropine is followed by a period of depression and paralysis of the peripheral nerve terminations resembling that seen under curare; after a few days there supervenes a stage of increased reflex excitability and tonic convulsions indistinguishable from those seen under strychnine. This stage slowly passes off and the animal again becomes normal.

Action.—These symptoms in man and other mammals, indicate stimulation of the **Central Nervous System** followed by depression. Those observed in man sometimes resemble those seen in the excitement stage of alcohol poisoning, and it has been suggested that in both the cause is rather a lessening of the control normally exercised by the higher powers over the lower motor areas than a true stimulation of the latter. But this is shown to be incorrect by the fact that in atropine poisoning the motor area is more easily stimulated by the

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electric current than normally. The stimulant action of atropine is also seen in the increased reflex response to irritation of the skin, as well as in the augmented activity of the centers in the medulla. The nervous symptoms under atropine, therefore, arise from true stimulation of the central nervous system, but they are wholly different from those produced by strychnine, because the latter acts especially on the lower parts of the nervous axis, while atropine acts more strongly on the higher divisions. The most marked symptoms of strychnine poisoning arise from the spinal cord and medulla oblongata, and consist in increased reflex movements and convulsions, while those caused by atropine are rather to be referred to the brain, and consist of increased coördinated movements, such as talking and delirium, the exaggerated reflex being of minor importance.

Atropine differs from caffeine, on the other hand, in its effect on the brain, for under the latter the psychical functions are those affected first of all. It would seem probable, then, that each of these drugs stimulates the whole of the central nervous system more or less, but that while strychnine acts more strongly on the lower divisions, the spinal cord and medulla, and caffeine on the highest functions, the psychical, atropine occupies a midway position, and exercises its chief action on the motor divisions of the brain. These are rendered so excitable that the controlling areas can no longer keep them in check, and an increase in movement occurs somewhat resembling that seen when the controlling areas are depressed by alcohol. The stimulant action spreads downward when large quantities have been absorbed, and involves the medulla oblongata and spinal cord, so that symptoms resembling those seen in strychnine poisoning may make their appearance. After the stimulation has lasted some time, depression sets in and may go on to complete paralysis of the central nervous system, which is fatal to mammals through cessation of the respiration. Even during the stimulation stage some symptoms of depression are to be made out, exactly as has been described under strychnine.

The peripheral action of atropine involves a number of secretory glands, organs containing unstriped muscular tissue, and the heart.

Generally this action can be described as a paralyzing action on the postganglionic terminations of parasympathetic nerves, and is an action antagonistic to that of the muscarine group. Atropine prevents the peripheral actions of acetylcholine, although it does not interfere with the liberation of acetylcholine which occurs at the nerve-ends upon nerve stimulation. It rather renders the tissues insensitive to the action of acetylcholine. Atropine acts on the terminations of some nerves (*e. g.*, to the sweat glands) associated anatomically with the sympathetic, rather than the parasympathetic, division, but in such cases there is reason to believe that these sympathetic nerves exceptionally transmit their impulses by discharge of acetylcholine, and that they are, in Dale's terminology, "cholinergic" rather than "adrenergic" nerves.

Most of the **Secretions** are decreased by the application of atropine —salivary, gastric, pancreatic, mucous, and sweat. This is due, not to any action upon the secretory cells, but to the failure of nervous impulses.

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It has been investigated most carefully in the salivary glands, but enough work has been done on the others to show that the process is the same in all. The *secretion of saliva* in the normal animal seems to occur only when impulses reach the gland cells by one of two paths—through the chorda tympani, or through the cervical sympathetic fibers. If the chorda tympani be divided and put on electrodes and a cannula be passed into Wharton's duct, a rapid flow of saliva occurs on stimulation of the nerve, which ceases or is very much diminished on stopping the stimulation. If now atropine be injected, stimulation causes no increase in the secretion, and atropine, therefore, seems to paralyze some part of the peripheral secretory apparatus. The chorda tympani passes through ganglion cells on its way to the gland cells, and the impulses might be hindered in their passages through these, as actually occurs under the action of some drugs. But this is not the explanation of the inefficiency of chorda stimulation, as is shown by the fact that if the electrodes be pushed into the hilus of the gland so as to stimulate the nerve fibers beyond the ganglia no secretion follows. Another explanation would be that the gland cells themselves are paralyzed by atropine, but this is shown not to be the case, for on stimulating the sympathetic, which supplies the same cells as the chorda tympani, the usual secretion follows. The site of action of atropine, therefore, seems to lie between the ganglion cells on the course of the chorda tympani and the secretory cells, that is, the point of attack is the terminations of the nerve fibers in the gland cells. The secretion of saliva seems to occur generally only on the arrival of impulses by way of the chorda tympani, so that on the paralysis of its terminations the secretion ceases entirely.

In the same way the other *glands of the mouth, throat, nose and respiratory passages* cease secreting after atropine, and the effect is the characteristic dryness of the mouth, the hoarseness of the voice, and the thirst and difficulty in swallowing complained of after its administration.

The secretion of the *gastric juice* has been shown to be diminished or entirely arrested by atropine, which paralyzes the terminations of the secretory fibers of the pneumogastric nerve in the stomach (Fig. 34, page 460). The hydrochloric acid of the secretion is more reduced than either the pepsin or the fluid as a whole. The secretion of *pancreatic juice* is reduced after atropine, and stimulation of the pneumogastric has no effect on it, while in the normal animal it accelerates the flow. The secretion induced by the specific pancreatic hormone, secretin, continues, showing that atropine does not act on the cells of the pancreas, but only isolates them from the pneumogastric nerve. But as the formation of secretin depends on the passage of hydrochloric acid into the duodenum, and this is lessened by the action on the gastric glands, the pancreatic secretion is further reduced in this indirect way.

The secretion of *tears* is diminished by atropine, presumably from the interruption of the nervous connections of the lacrimal glands. The flow of *bile* is also somewhat lessened but the interchange of glycogen and sugar in the liver is not affected by atropine.

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The same paralysis is produced in the terminations of the nerves in the *sweat glands*. Stimulation of the sciatic nerve as a general rule causes perspiration in the foot of the cat and dog, but after atropine this effect is absent, because the impulses cannot reach the cells through the paralyzed terminations, and the skin therefore becomes dry and hot. The local application of atropine to the skin has no effect on the sweat secretion, as it does not penetrate to the glands. The secretion of *milk* is not materially changed by atropine, whether the alkaloid is carried to it by the blood or is applied locally. This is in accord with the physiological observation that the mammary gland continues to secrete after all its nerves have been cut and allowed to degenerate; in other words the mammary secretion is largely independent of the nervous system.

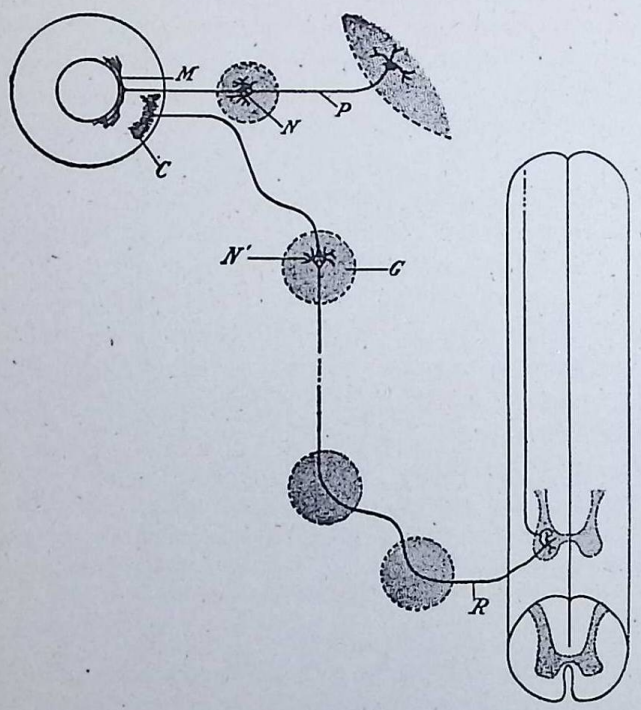

FIG. 35.—Diagram of the innervation of the iris. *P*, A fiber of the motor oculi passing from the brain to the ciliary ganglion (*N*), in which it terminates around a nerve cell, which sends an axis cylinder to terminate, *M*, in the circular fibers of the iris. *R*, A sympathetic nerve fiber issuing from the lower cervical cord, running through the stellate and inferior cervical ganglia and terminating around a ganglion cell in the superior cervical ganglion, *G*. The axis cylinder from this nerve cell runs to the iris (passing the ciliary ganglion) and terminates, *C*, on the radiating fibers. *M* is the point acted on by atropine and muscarine. *N*, *N'*, The ganglion cells, are the seat of action of nicotine. *C*, The terminations in the dilator fibers, that of epinephrine.

The *kidney* is not controlled by secretory nerves, and atropine causes little or no change in the amount of urine except through the arrest of the other secretions. The *secretion of lymph* is not altered by atropine, so that it also is not controlled by nerves in the same way as the true secretions. The secretion of the suprarenal glands is stimulated by atropine to a slight degree.

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All **Organs Containing Unstriped Muscle** (apart from the arterial wall) seem to be altered by atropine. Thus the movements of the pupil and esophagus (except in animals in which these consist of striped muscle), stomach, intestine, bladder, uterus, spleen and thoracic duct are affected by atropine.

The dilatation of the *pupil* occurs on internal administration as well as on the application of minute quantities locally, and is due to paralysis of the myoneural junctions in the circular muscle of the iris. This is shown by the fact that stimulation of the motor oculi nerve or of the postganglionic fibers from the ciliary ganglion is without effect. This limits the paralysis to the periphery, and that the muscle is not acted on is shown by its reacting to electrical stimulation. The local nature of the action may be further shown by carefully applying a minute quantity of the drug to one side of the cornea, when dilatation of one half or less of the pupil occurs, the rest remaining contracted. The motor oculi (Fig. 35) constantly transmits impulses through the ciliary nerves to the sphincter muscle of the iris and keeps the pupil moderately contracted, and when these impulses can no longer reach the iris owing to the interruption of the path, the sphincter relaxes and the pupil dilates. The contractile substance does not seem to be affected by the ordinary application of atropine, but if strong solutions be continuously applied, it may be paralyzed by it as by many other drugs. Atropine antagonizes the action of pilocarpine in the pupil after degeneration of the motor oculi, and the receptor for these alkaloids therefore does not undergo degeneration and must be situated in the muscle between the nerve ends and the contractile substance.

The constrictor muscle is constantly opposed by dilator fibers, and when the former is thrown out of activity by the paralysis of the terminations of the motor oculi, the radiating fibers cause an active dilatation. If, however, the radiating muscular fibers be separated from their innervating center by section of the cervical sympathetic nerve in the neck, they also cease to contract and there is no active dilatation, so that atropine causes less widening of the pupil than it would if impulses continued to reach the radiating muscle. After the application of atropine to the eye, the iris often relaxes with sufficient force to tear weak adhesions to the lens, and if the iris be attached at two points to the lens, atropine causes a bow-shaped dilatation between them, the concavity being directed inward. The dilatation is therefore an active movement, accomplished by the contraction of the radiating muscular fibers, but these are not put in motion by the action of atropine on the radiating muscles of the iris, or their nerves, but by the normal impulses descending from the central nervous system, which after atropine are not counterbalanced by impulses reaching the circular fibers.

The dilatation of the pupil effected by atropine is not quite maximal, for stimulation of the cervical sympathetic trunk generally increases it, though but slightly. It differs considerably in different animals, being more complete in man, the dog and the cat than in the rabbit, entirely absent in birds and reptiles, and elicited with difficulty in the frog. In birds and reptiles the iris consists of striped muscle fibers, and accordingly atropine has no action on the nerve terminations.

When complete dilatation is attained, the pupil ceases to contract in bright light, as the impulses descending from the central nervous

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system are prevented from reaching the muscle, although the rest of the reflex arc is intact. The retina is unprotected from bright light and this often gives rise to pain and discomfort in the eyes and headache.

Besides the dilatation of the pupil, a further result of the application of atropine to the eye is the paralysis of the *accommodation*. Near objects are no longer seen clearly, while distant ones are as distinct as formerly or may be even more distinct to some eyes. The action is here again on the myoneural junction, in this case in the ciliary muscle. On local application the paralysis of accommodation occurs later, and disappears earlier, than the dilatation of the pupil, and larger quantities are required to produce it.

FIG. 36

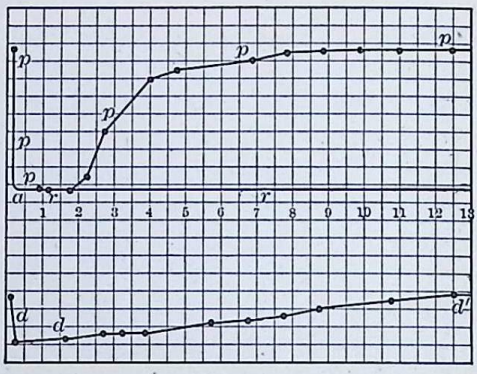

FIG. 37

FIGS. 36 and 37.—Charts of the changes in the accommodation (*pp*) and in the pupil (*dd*) under atropine. The impairment of the accommodation and the widening of the pupil are indicated by downward movements of the lines, while the return to the normal is shown by an upward movement. In Fig. 36 the time from the application of atropine is given in minutes to show the beginning of the action; in Fig. 37 the time is in days to show the gradual recovery. (After Donders.)

The *intra-ocular pressure* appears to be unchanged by atropine in the normal eye, but when there is a tendency to hypernormal pressure, atropine often augments it considerably, whether it is applied locally or is carried to the eye by the circulation. This is apparently the indirect result of the dilation of the pupil, by which the lymph outflow is obstructed; in the normal eye this is not sufficient to raise the pressure, but in eyes in which the outflow is already deficient the additional hindrance may suffice to increase the tension and precipitate an attack of glaucoma.

The *bronchial muscle* normally contracts when the pneumogastric nerve is stimulated, but makes no response after atropine, which paralyzes the myoneural terminations; the sympathetic fibers which inhibit the bronchial muscle and dilate the bronchi are unaffected by atropine.

The terminations of the nerves in the unstriped muscle of the *esophagus* are affected in the same way as in the bronchial muscle. A curious contrast was noted by Luchsinger in the behavior of the esophagus in rabbits and cats, in the former of which the muscle is striated, while in the latter the upper part is striated, the lower is unstriated. Atropine,

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he found, paralyzes the vagus in those parts which are unstriped, while leaving unaffected those in which the fibers are striped. Exactly the opposite occurs after curare, which paralyzes the nerve supply of the striped muscle, while leaving the unstriped active.

It is possible that the difficulty in swallowing, which is present in cases of poisoning by atropine, may be due in part to the paralysis of the motor nerve, but it is generally attributed to the absence of the mucous secretion and consequent dryness of the passages.

Atropine has generally a sedative effect on the movements of the *stomach* and *intestine*, though vomiting has sometimes been observed in cases of poisoning, and less often free evacuation of the contents of the bowel. After very small quantities the normal peristalsis is not affected, and the movement induced by ordinary doses of the purgatives is not arrested, but the griping pains resulting from large doses or from the more violent purgatives are absent or less marked if atropine is given along with them. Similarly, the violent peristaltic and tetanic contractions seen after such poisons as pilocarpine and muscarine are prevented by the preliminary injection of atropine.

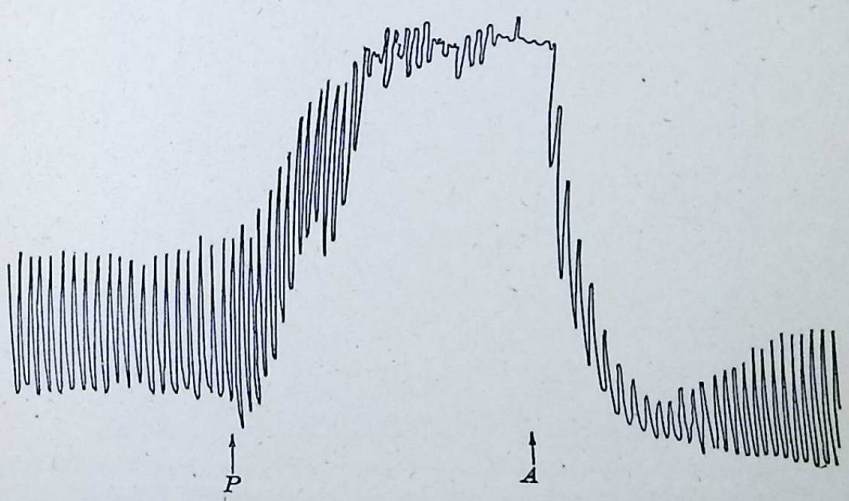

FIG. 38.—Movements of the intestine. At *P*, pilocarpine causes a violent tetanic contraction, which is maintained until at *A* atropine is applied, when the spasm is immediately relieved. The normal pendulum movements continue afterwards. (Magnus.)

These results suggested that atropine paralyzes the terminations of some of the extrinsic nerves of the stomach and bowel in the same way as it paralyzes the oculomotor terminations in the iris. But this proves to be incorrect, for the vagus and splanchnic nerves continue to exert their ordinary influence after atropine. In fact, these small doses of atropine appear to arrest only certain abnormal violent forms of contraction, and as they do this without interfering with the normal peristalsis and without interrupting the path of nervous impulses from the brain to the bowel, it must be accepted that these abnormal forms arise from some mechanism which is distinct from that presiding over the ordinary peristalsis, and which does not lie on the path of the nerve impulses.

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This action on abnormal contractions is the only one induced by therapeutic doses of atropine, but in animal experiments large quantities tend to increase the peristalsis from some action exerted on the plexus of Auerbach (Magnus). It is possible that this increased peristalsis may account for the vomiting and purging sometimes seen in cases of poisoning. Finally, very large quantities paralyze the muscle fibers, but this probably does not occur in the intact animal.

Atropine exercises the same sedative effect on the movements of other organs as on those of the bowel. Thus, the *spleen, uterus, gall-bladder, ureters, urinary bladder* and the *other ducts* of the genito-urinary tract react like the stomach and bowel, several poisons failing to induce contractions after atropine, while stimulation of the nerves continues to be effective. It has been observed frequently in cases of poisoning that the urine is ejected soon after the ingestion of the poison, and subsequently there is a desire to micturate without the ability to do so.

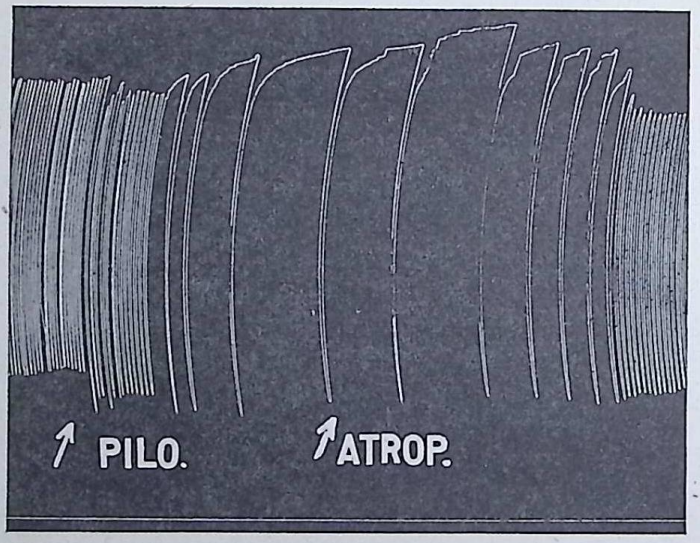

FIG. 39.—Tracing from heart of a turtle showing the effect of pilocarpine and atropine applied directly to the heart. Rather slow absorption. Lever moves down in systole.

Atropine paralyzes the **Inhibitory Terminations of the Vagus in the Heart,** and stimulation of this nerve therefore causes no change in the pulse after its administration. Nicotine in large doses also removes the inhibitory power of the vagus, but acts on a different part of the nerve, namely, on the ganglia. That atropine does not act here but on the terminations has been shown by a number of observations. Thus, in the normal frog's heart, and even after paralysis of the ganglia on the course of the vagus, electrical stimulation of the sinus venosus causes slowing and standstill of the heart, because the stimulus reaches the postganglionic nerve fibers (Fig. 32, page 431); but after atropine, no slowing follows stimulation of the sinus. Again, several drugs stimulate the ends of the vagus in the heart and act on parts in which no ganglia exist, but these drugs have no effect whatever after atropine. Small quantities of atropine have no further action on the heart than

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the paralysis of the inhibitory nerve ends. The terminations of the accelerator nerve are unaffected, exactly as the terminations of the sympathetic in the salivary glands, and the heart muscle is neither stimulated nor depressed. The heart is therefore placed in the same position as if the vagus were divided in the neck, and, accordingly, it is accelerated in some animals, while in others the rhythm is unchanged. In the dog there is marked quickening of the heart after atropine, because normally impulses are constantly transmitted from the inhibitory center in the medulla, and these prevent the heart from beating as rapidly as it would if freed from the nervous control. In the cat the tone of the vagus is less, and the changes produced by atropine are correspondingly smaller, while in the rabbit and frog there is generally no inhibitory retardation of the heart, and atropine therefore produces little change. In man the effects vary considerably with the age of the patient. The inhibitory fibers seem almost inactive at birth, but their tone increases with age up to twenty-five to thirty-five years, and from this time lessens again. Atropine does not quicken the heart in the newborn child, but up to about thirty the acceleration increases with the age, and from this point onwards it lessens again until the heart is accelerated by only 4 to 5 beats per minute in patients between eighty and ninety years. Along with the acceleration of the pulse the other effects of vagus section are also produced—increase in the extent of systole, decrease in the diastole and augmentation of the output of the heart per minute.

Stimulation of the vagus causes no retardation of the pulse after an ordinary dose of atropine, but, on the contrary, is not infrequently followed by acceleration from the presence of accelerator fibers which are not affected by atropine. But it is found that if a minimal amount of atropine is given, so that slight vagus stimulation has no effect, a very strong current may still slow the heart; the terminations are so weakened that feeble impulses fail to reach the heart, but strong impulses can still force their way through the block. (Pilcher and Sollmann.)

Large quantities of atropine, besides paralyzing the vagus, weaken and depress the heart muscle, and the contractions consequently become slower and weaker and the output of the heart is less than normal. Even therapeutic doses injected hypodermically in man slow the pulse for a short time, possibly from direct action on the heart muscle, but more probably from stimulation of the vagus center before the nerve terminations are paralyzed; the first effect is thus a fall in the pulse rate followed by marked acceleration.

The **Peripheral Action** of therapeutic doses of atropine is due to its paralyzing receptors in a number of organs. Some of these are normally put in action by nerve impulses, which they transmit to the contractile or secretory cells, and their paralysis by atropine leads to the failure of part of the nervous control of the organ (many glands, pupil, bronchial muscle, esophagus, and heart). In other organs the receptors do not lie in the path of nerve impulses and their paralysis by atropine therefore does not affect the nervous control of these organs (muscle of stomach, intestine spleen, uterus, and bladder). The effect of atropine on these organs is in fact only detected by the cessation of unusual movements induced by certain poisons and by some pathological conditions (see also muscarine and pilocarpine, page 440). The organs thus affected receive their innervation from the

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autonomic system, and, with few exceptions, from the parasympathetic division. Atropine prevents the actions of acetylcholine on parasympathetic nerve ends by preventing the action of acetylcholine on the effector cells.

The voluntary **Muscles** are not directly affected by atropine. An action similar to that of curare is seen in the frog under large doses. In mammals the twitching induced by physostigmine through its action on the myoneural junctions is, according to some authors, antagonized by large doses of atropine; but no true curare action is induced by atropine in mammals.

The terminations of the **Sensory Nerves** are depressed by its local application. Thus, when atropine is applied to an irritated surface of the skin or to a mucous membrane, numbness is produced and the sensation of pain is lessened; no such effect occurs when atropine ointment is rubbed on the unbroken skin and the local anesthetic effect is not elicited by its internal administration.

Circulation.—The changes in the circulation under atropine arise for the most part from the changes in the heart. The blood-pressure often falls for a few minutes at first and then rises above the normal from the acceleration, when this is marked. But the rise in pressure from the acceleration is not great unless there is unusual activity of the inhibitory mechanism previously. There is no evidence that the vasoconstrictor center in the medulla is excited by atropine. In normal animals there is thus no evidence that atropine acts on the vessels or on the nerve ends in them; but in animals whose vessels are dilated by acetylcholine, atropine immediately counteracts this effect, which indicates that it possesses some vascular action. Very large amounts of atropine depress the heart and consequently the blood-pressure falls; the respiration fails in cases of poisoning before the heart is seriously injured. In poisoning there is often flushing of the skin of the head and neck and a rash resembling that of scarlet fever, and these have been regarded as due to dilatation of the arterioles from stimulation of the vasodilator center; the flush is said to disappear on section of the cervical sympathetic cord, which would suggest its central origin. The rash usually disappears after a few hours, but is sometimes followed in a day or two by desquamation.

The action of atropine on the **Respiration** has been the subject of much discussion. In therapeutic doses, its only effect is to relax the bronchi, and the respiratory center is unaffected; larger amounts accelerate the breathing from stimulation of the center and increased formation of carbon dioxide. In severe poisoning this quickened breathing is frequently interrupted by convulsive movements, and such an interruption often proves to be final. If it returns, the movements become shallower and slower in the stage of depression of the nervous centers, and the failure of the respiration is the cause of death in fatal cases of poisoning.

Atropine often induces a marked rise in **Temperature**, due in part probably to the fact that the body heat is not dissipated as a result of the inhibition of activity of the sweat glands and also because of a direct action on the heat centers of the brain.

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Distribution and Excretion.—Atropine is rapidly absorbed and may be found in most organs. It is excreted in the urine in man and most animals, partly as unchanged atropine, partly broken up into tropine; from a third to a half of that ingested reappears in the urine, and traces have been found in the milk and also in the fetal blood. The rest of the atropine undergoes oxidation in the body, apparently in the liver; in some rabbits, which show a very high congenital tolerance, much of the atropine ingested undergoes decomposition in the blood plasma, being apparently hydrolyzed into tropine and tropic acid. In other rabbits no such action occurs in the blood and these do not acquire this power even when treated for a long time with atropine; they may be endowed with it, however, by the injection of the serum of an an mal which already possesses it, and even cats which do not normally destroy atropine in the plasma are also enabled to do so by the injection of the active serum of a rabbit (Schinz); the blood of man, the dog and many other animals does not seem to possess this property.

Tolerance.—Most animals withstand much larger quantities of atropine than man, and an especial degree of tolerance is met with in the herbivora; rabbits, for example, may be fed for weeks on belladonna leaves without showing any symptoms; this is undoubtedly the result of the active decomposition of the alkaloid which occurs in their plasma. It has also been observed that the action of atropine on the heart and other organs passes off more quickly in rabbits than in other animals and this again arises from the atropine being destroyed so rapidly. A certain degree of tolerance may be acquired by other animals through the continued administration of atropine, which ceases to elicit the symptoms from the central nervous system in the doses previously sufficient and later seems to have a weaker and shorter action on the peripheral organs.

In his studies upon the rôle played by the liver in the disposal of atropine and indirectly upon the question of tolerance, De Saram found that the amount of atropine which could be tolerated by rabbits, if the injection were made into the portal vein, was about twice the amount which would prove fatal if it were injected into an ear vein. He concludes, therefore, that the liver is important as a detoxifying agent.

Hyoscyamine is rarely obtainable in pure form, as it is almost always mixed with atropine, into which it changes when kept in solution and perhaps even when dry. It paralyzes the same peripheral mechanisms as atropine, but acts almost exactly twice as strongly on them. Its action on the central nervous system in mammals resembles that of atropine and the fatal dose is the same, but in the frog it has less tendency to cause convulsions. No narcotic influence is exercised on either frogs or mammals; the belief that it induces sleep is founded on observations in which scopolamine was mixed with the hyoscyamine employed.

The action of atropine, as has been stated, is compounded of that of natural or levorotary hyoscyamine with that of its dextrorotary isomer. The latter does not exist free in nature and possesses little or no action on the nerve terminations, while it stimulates the spinal cord of the frog more than either atropine or hyoscyamine. The peripheral action of atropine is thus due to

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its containing *l*-hyoscyamine, and as a grain of atropine contains only half a grain of *l*-hyoscyamine, the former naturally exercises only half the effect of a grain of *l*-hyoscyamine. On the other hand, the half grain of dextrorotary hyoscyamine in a grain of atropine is almost inert on the nerve terminations, but exercises the same effect on the central nervous system as its levorotary complement. Atropine thus acts on the central nervous system in mammals in the same strength as hyoscyamine, but only half as strongly in the periphery.

Von Oettingen and Marshall found that the ratio of potency of atropine and its two isomers differed according to the species of animal employed, and the structure studied, and even that sera of different rabbits varied in their ability to destroy the alkaloids. They explain this as being due, in part at least, to the relative rates at which the alkaloids are destroyed in the body. They showed that rabbit serum may destroy the levohyoscyamine the most rapidly of the three alkaloids and the dextrocompound more slowly than the racemic atropine which stood intermediate in this respect. Thus there might be quite a variation in responsiveness of different rabbits to these alkaloids and therefore to the relative ratio of potency assigned to the different members of the series.

Scopolamine or **Hyoscine** resembles atropine closely in its peripheral action, except that it passes off more quickly. The inhibitory terminations in the heart are paralyzed; but the therapeutic dose in man is too small to elicit this effect, and the pulse is therefore unaltered in rate or may be slower, owing to the hypnotic action. Applied to the conjunctiva it produces mydriasis and loss of accommodation more quickly than atropine, but for a much shorter time; pure scopolamine acts about twice as strongly on the nerve terminations as atropine, or about equally as strong as hyoscyamine. The effects on the central nervous system present the greatest divergencies from those described under atropine, for the characteristic stimulation is absent in the great majority of cases. As a general rule, scopolamine produces a marked sensation of fatigue and drowsiness, the patient moves about less and speaks less, and a condition in no way dissimilar to the natural sleep follows. In many cases, however, a short stage of excitement with giddiness, uncertain movements and difficult and indistinct speech precedes sleep, and occasionally symptoms exactly resembling those produced by atropine follow the administration of scopolamine, especially if large doses are employed. Sleep generally lasts from five to eight hours, and the patient may then remain quiet for several hours longer. As a general rule, after small doses no confusion is complained of on awakening, but dryness of the throat and thirst are often present. Larger doses do not cause deeper sleep but give rise to delirium and excitement resembling those following atropine. In one or two cases collapse has been observed after scopolamine. The respiratory center does not seem to be stimulated as by atropine, the respiration generally becoming slower from the beginning.

In the lower mammals scopolamine reduces the excitability of the motor areas as tested by electric shocks, while the reflex excitability in the frog is not increased as by atropine. Scopolamine appears to be excreted or destroyed in the tissues much more rapidly than atropine, for its effects last a shorter time.

The action of scopolamine, then, seems to correspond with that of atropine, save that the central nervous system is here depressed, while the action on the peripheral nerve ends is of shorter duration. It depres-

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ses the brain in very small quantities, ½ mg. being generally sufficient to induce quiet. The therapeutic dose is well below the fatal dose, but medicinal doses occasionally produce toxic symptoms, apparently a form of idiosyncrasy. A certain degree of tolerance is produced after repeated use, so that the dose has to be increased after a week or two.

Scopolamine is much less reliable as a hypnotic than morphine or the members of the chloral group. It is most effective when sleep is prevented by motor excitement, and the sleep seems to arise from the relief of this condition and not from depression of the consciousness.

Scopolamine is levorotary to polarized light; the racemic form, which is often present in commercial scopolamine, acts only one-half as strongly on the peripheral organs, because in it the levorotary alkaloid is mixed with the dextrorotary isomer, which is almost inactive. The cerebral action is equal, however, in the two forms.

Scopolamine has been used in the preparation of patients for general anesthesia, as already described on page 309. However, the dangers associated with its use has militated against its wide employment for this purpose.

Scopolamine is useful in the prevention of travel-sickness being used for this purpose to prevent seasickness and airsickness during the late war. It is available commercially in the form of tablets containing 0.1 mg. of scopolamine camphorate and 0.4 mg. hyoscyamine camphorate and as suppositories containing twice as much of each drug.

Scopolamine is useful in the treatment of postencephalitic Parkinsonism in doses of 0.65 mg. four times a day. There is often a marked alleviation of the psychic symptoms and psychomotor excitement. Similarly in infantile cerebral palsy scopolamine may be helpful in overcoming the spastic paralysis, tremor and athetoid movements.

Following the administration of scopolamine, the normal plantar response becomes extensor (Babinski sign) and the administration of this drug has therefore been advocated for unmasking concealed damage to the pyramidal tract which is manifested by an extensor plantar response.

Genoscopolamine, an amino oxide of scopolamine is also available commercially as a substitute for scopolamine.

The other natural alkaloids have been less carefully examined than the three foregoing and possess no therapeutic interest.

Homatropine and other Artificial Tropeines

Among the artificial tropeines, **Homatropine**, a compound of tropine and mandelic acid, resembles atropine in its action but is much less poisonous. When applied to the eye, it dilates the pupil almost as rapidly as atropine, but less completely, and the action passes off much sooner. It has less tendency to increase the intra-ocular tension than atropine owing to its shorter action.

Eumydrine, the methyl nitrate derivative of homatropine, has been used to some extent in ophthalmology. Its mydriatic action is more prompt and less enduring than that of atropine and it is less poisonous.

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Novatropine (Homatropinemethylbromide) was introduced as a substitute for atropine in the treatment of gastro-intestinal spasm and hyperchlorhydria. It is less toxic than atropine, its cerebral effects are less marked and side effects, such as cycloplegia and dryness of the mouth and skin, are also less pronounced. The ratio of toxicity of atropine to novatropine as reported by different investigators has differed somewhat, but it would seem to be in the neighborhood of 1 to 33. Slight cerebral symptoms have resulted from the use of maximum doses, but no cumulative effects have been reported. Novatropine is a white crystalline powder easily soluble in water and is usually prescribed in tablet form, each tablet containing 2.5 mg., 1 to 2 tablets being taken three times daily before meals.

The other synthetic substitutes which are not members of the tropeine alkaloids are discussed later (page 482).

The other tropeines vary in their action on the lower animals, some of them failing to act on the peripheral organs, while others have the peripheral action of atropine but in a weaker degree; the compounds of tropine with the acids of the methane series possess much less peripheral atropine action than the others. The peripheral action is most developed in the compounds of tropine with acids of the benzene series possessing hydroxyl and an asymmetric carbon atom, the whole molecule being levorotary. A considerable variation also exists in the effects of the tropeines on the central nervous system, some causing excitement like atropine, while others act as depressants and therefore resemble scopolamine.

Tropine itself is a weakly toxic, basic substance, which in large quantities stimulates the frog's heart, but does not paralyze the vagus nor the oculomotor terminations on local application. After the injection of large quantities, dilatation of the pupil has been observed, it is true, but this does not seem to be of the same origin as that produced by atropine.

Some synthetic scopoleines have been found devoid of action on the nerve ends in the pupil and heart and on the salivary secretion. They possess a certain stimulant effect on the heart muscle like some of the synthetic tropeines, and all produce more or less depression on the central nervous system and narcosis.

The action of the **Crude Drugs** is very similar to that of the active principles already discussed. The peripheral action of all of them is therefore almost identical in kind, though varying in degree. In considering their effects on the central nervous system it must be remembered that preparations containing much atropine are more stimulant, those with scopolamine more sedative. But as the relative amount of the different alkaloids changes with various conditions such as the age of the plant and the methods of preparation, it is obvious that accurate results can be obtained only by the use of the pure principles. Even when a preparation is accurately standardized in the content of alkaloids, as in the U. S. P. and B. P., its power may vary very widely according to the proportion of levorotary alkaloid (hyoscyamine) to racemic (atropine).

Therapeutic Uses.—The numerous changes produced by atropine and its congeners on the organism would indicate for them a very wide sphere of usefulness were it possible to elicit their action on one organ without affecting others, and this difficulty is being overcome to a certain extent as the different individuals of the series have been more carefully compared, and new tropeines and other modifications of the tropine radical are being made available in therapeutics.

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The peripheral action of the natural alkaloids of the group is so uniform that any member might be used to elicit it, but the only one that has come into general use for its peripheral effects is atropine. The purposes for which atropine is employed may be divided into groups as follows:

To Arrest or Lessen Secretions.—In rare cases of excessive *salivation* atropine has proved of service, and it may also be used to lessen the *perspiration*. For this purpose comparatively small quantities, such as a $\frac{1}{4}$ mg. (1/250 gr.) given by the mouth or hypodermically, are generally sufficient, or the extract or tincture of belladonna may be used instead. Applied locally in the form of an ointment, liniment, or plaster, atropine is without effect. Some forms of excessive secretion of *gastric juice* have been treated by atropine usually in the form of the tincture of belladonna. It is also of value in *bronchitis* with profuse expectoration and is used in combination with morphine in edema of the lung.

Agaricin, derived from white agaric (*Agaricus albus*, *Boletus laricis*), a fungus growing on the European larch tree, was formerly used as an antihydrotic. Its active constituent is agaric acid, $C_{16}H_{30}O_5$. It acts on the terminal nerve endings of the sweat glands, but unlike atropine has no effect on other secretions (saliva, tears, etc.), or upon the nerve endings in the heart and pupil.

To Paralyze the Cardiac Inhibitory Terminations.—For this purpose a slightly larger quantity is required than is necessary to stop the secretions, and the administration of sufficient atropine to paralyze the vagus (1 mg.) therefore involves unpleasant dryness of the throat and difficulty in swallowing. In cases where slowing of the heart tends to be dangerous in itself, more especially in poisoning with muscarine, pilocarpine and their allies, atropine is indicated. It may also be used for diagnostic purposes, to find if bradycardia is due to disease of the heart muscle or to inhibition. The resultant quickening is much less in old than in middle-aged people, and in many cases of old aortic lesion the administration of atropine is followed by little acceleration. In typhoid fever atropine accelerates the pulse comparatively little owing to the heart muscle being involved in the action of the toxin. The use of atropine to paralyze the vagus terminations in the bronchi before the administration of an anesthetic has been discussed already (see page 307).

To Paralyze the Terminations of the Motor Nerves in the Iris and Ciliary Muscles.—It is used for this purpose largely in ophthalmology as a means of diagnosis and of treatment, and the precise conditions in which it is indicated may be treated better in textbooks on this subject than here. For these objects, solutions of the alkaloidal salts are generally applied to the conjunctiva, when enough of the alkaloid diffuses into the eye to produce marked local effects without affecting more distant organs. In order to dilate the pupil, extremely dilute solutions are used; a few drops of a solution of 1 in 1,000, or even of 1 in 10,000 are quite sufficient. Much stronger solutions are required to paralyze the accommodation, and as a general rule 1 per cent is used. These strong solutions produce complete paralysis in one-half to one hour, and the accommodation does not recover completely until after

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five to seven days, while the pupil may not regain its normal size for ten to fourteen days. The application of even weaker atropine solution renders the sight imperfect for an inconveniently long period, and hyoscyamine and homatropine are therefore much used in its stead. The symptoms produced by a 1 per cent solution of homatropine pass off or, at any rate, become very much less marked in the course of thirty-six hours. These are consequently preferable for diagnostic purposes, while atropine is rather to be used where it is desirable to produce a paralysis of longer duration, as in various inflammatory conditions of the iris or cornea. Atropine is also preferable where complete paralysis of the accommodation is necessary, as homatropine often fails to effect this. Atropine and its congeners are contraindicated where there is any suspicion of glaucoma, as, owing to their action on the intra-ocular pressure, they may either aggravate the disease already present or precipitate an acute attack.

When dilatation of the pupil is necessary and there is reason to apprehend the results on the intra-ocular pressure, homatropine should be employed, as its effects can be readily controlled by eserine. Numerous cases of poisoning have arisen from the extensive use of atropine in disease conditions of the eye. It is often asserted that it passes down with the tears through the lacrimal duct and is absorbed from the nose, throat and stomach, but it may be absorbed from the conjunctiva itself. The symptoms are generally only the milder ones of atropine poisoning—dryness of the throat and slight excitement—but dangerous and even fatal poisoning has also arisen from its local application. In many cases this is due to the application of unnecessarily strong solutions to the eye, but, on the other hand, some patients seem abnormally sensitive to the action of atropine, and scopolamine 0.5 per cent or homatropine, ought to be preferred. In rare cases a curious inflammatory condition of the conjunctiva is set up by atropine, and this is often supposed to be due to the use of irritant preparations, but sometimes seems to follow the application of the absolutely pure alkaloid, and is apparently an idiosyncrasy; it may, perhaps, be explained by the arrest of the ordinary secretions of the lacrimal gland and conjunctiva in these cases. Sometimes discs of gelatin impregnated with atropine or homatropine (B. P.) are applied to the conjunctiva instead of solutions of the salts.

To Relax Spasm of the Stomach and Intestines.—In various forms of colic, atropine is of very great service in lessening pain and allowing the passage of the intestinal contents; for instance, it is preferable to morphine in lead colic, as it does not cause constipation. It sometimes relieves the pain of gastric ulcer by preventing the reflex contraction of the stomach wall, and similarly spasmodic contraction of the pylorus may be released. Belladonna in the form of the extract is often prescribed along with purgatives in order to lessen the griping which they produce, and has been used as a laxative in some forms of constipation with considerable success. The object of prescribing an impure preparation instead of the alkaloid is to allow of a strong local action on the

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intestinal wall along with a slow and imperfect absorption, as the pure alkaloidal salts are liable to be absorbed in the duodenum.

To Relax Spasms of the Involuntary Muscles of Other Organs.—In the spasmodic contraction of the ureters and bile ducts due to calculi, atropine is occasionally prescribed either in the form of a pill or in solution for internal use, or by hypodermic injection. In some forms of asthma due to contraction of the bronchial muscles, atropine has been applied locally by means of a spray or given internally. Perhaps this action in relaxing spasmodic contractions may also explain the beneficial effects obtained in cases of incontinence of urine in children, in which belladonna has long been used.

To Lessen Pain.—Belladonna liniment, plaster and ointment formerly enjoyed a reputation as local anodynes, but are now rarely used and are of doubtful efficiency.

The Effects on the Central Nervous System of the members of this group are very different, and the purposes for which they are used are diametrically opposed. Atropine is used as a stimulant in various conditions of depression of the brain and medulla oblongata. Thus, in collapse its hypodermic injection has been advocated to stimulate the respiration. In dangerous poisoning from narcotic and hypnotic drugs, more especially in opium poisoning, atropine has been largely used. It may be questioned whether atropine may not be replaced by caffeine with advantage. The former stimulates the medullary centers, but subsequently paralyzes them, while caffeine, even in comparatively large quantities, does not seem to have a depressant action in man.

In some spasmodic diseases, such as whooping-cough, belladonna preparations have long enjoyed a wide reputation; this may possibly be explained either by the scopolamine reducing the excitability of the respiratory center, or by atropine relaxing bronchial spasm.

Scopolamine or *hyoscine* has been used as a narcotic to depress the central nervous system; it is of great efficacy in *insanity*, producing sound and refreshing sleep, but is of less value in controlling the excitement during the day, and may in fact increase it. Scopolamine is also used with benefit in various forms of *tremor of central origin*, and is said to lessen sexual excitement. Its hypnotic action does not seem to be of the same nature as that of opium, for in sleeplessness produced by pain it is of comparatively little value, and it has no power to relieve pain itself. It differs from chloral in not inducing deep sleep, for patients under the influence of scopolamine can always be aroused and are much less confused than after chloral. The special indications for scopolamine seem to be sleeplessness due to abnormal activity of the motor areas and some forms of tremor.

It is very useful in relieving the tremor of *paralysis agitans*. In post-encephalic *Parkinsonism* it often produces a remarkable improvement: diminution of the generalized muscular rigidity, lessening of the tremors of the face and extremities, disappearance of excessive lacrimation and salivation, improvement of speech and a general brightening of the mental outlook. It is usual to commence with small doses, *e. g.*, 0.4 mg. per day subcutaneously, which may be gradually increased to

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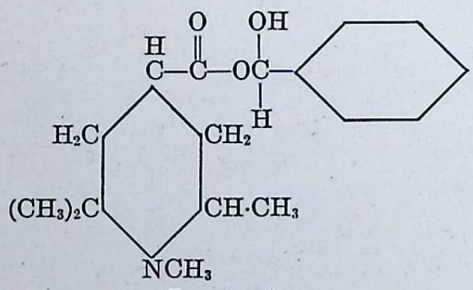
1 mg. or more, if required. By mouth, larger doses are required. Preparations of stramonium have also been extensively used for this purpose.

On the use of scopolamine with morphine as a surgical anesthetic see page 353.

Poisoning.—In cases of poisoning with belladonna and its allies the treatment is purely symptomatic. In the excitement stage sedatives may be used; perhaps chloroform and ether are best, as their effects are more transient than the others. Morphine has been advised, but its action on the respiratory center renders its use dangerous, as in severe atropine poisoning the stimulation soon passes into depression, and the effects of the poison and its so-called antidote therefore supplement each other. Chloroform and ether, on the other hand, may be used to control the spasms and then stopped when these pass off. In the depression stage caffeine may be used, and eventually artificial respiration. Pilocarpine is of course useless, as it does not antagonize the actions of atropine on the central nervous system, which is the point of danger.

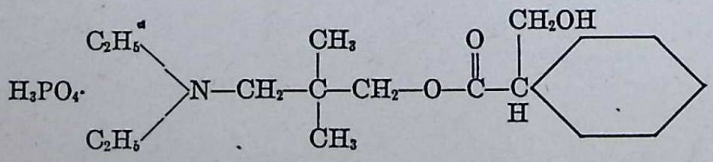
2. Other Synthetic Substitutes for the Belladonna Alkaloids

In addition to the synthetic tropeines already discussed, several simpler compounds have been introduced as substitutes for atropine.



Eucatropine

Eucatropine, introduced under the trade-name euphthalmine, is the mandelic acid ester of a polymethyl piperidine derivative. It is used in the form of the hydrochloride in a 5 to 10 per cent solution as a mydriatic. For this purpose 2 to 3 drops are instilled into the eye. Eucatropine induces prompt mydriasis without pain or corneal irritation. Like other mydriatics it may precipitate glaucoma in those predisposed to this condition. It does not affect the accommodation of the eye and its effects are of brief duration. It is useful in ophthalmoscopic examinations.



Syntropan, the tropic acid ester of 3-diethylamino-2, 2-dimethyl-1-propanol is used as a substitute for atropine, especially for those pur-

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poses for which an action on smooth muscle is concerned. For most animals it is less toxic than is atropine. Its mydriatic action on the eye of the cat is much weaker than that of atropine, as is also its action in suppressing salivation. Its action as a depressant of the parasympathetic nervous system is also much weaker than is that of atropine. However, as a depressant of spasm of smooth muscle, its potency approaches much closer to atropine in that it not only possesses an action on the nervous mechanism similar to that of atropine, but also exerts a direct action on the muscular tissue itself. This drug is therefore useful in cases of spasm of smooth muscle and is recommended in gastric spasms in colic due to cholelithiasis and in spastic conditions of the bladder and ureters.

Syntropan is a white crystalline powder soluble in water. It is administered in 50 mg. doses in tablet form—1 tablet being given three or four times daily. It can also be given by intramuscular or subcutaneous injection in 10 mg. doses.

Trasentin, $(C_2H_5)_2.NCH_2.CH_2.OOC.CH.(C_6H_5)_2$, an ester of diphenyl acetic acid and diethylamino ethanol is another synthetic non-official drug which has been advocated as a substitute for belladonna in the relief of spasm of the gastro-intestinal tract, uterus, ureter, etc. It is administered in the form of 75 mg. tablets or injected.

Preparations

U. S. P.

Belladonnæ Folium, the leaves of Atropa belladonna, containing 0.3 per cent of alkaloids.

Extractum Belladonnæ (1.25 per cent). Dose, 15 mg.

Tinctura Belladonnæ (0.03 per cent). Dose, 0.6 cc. (10 min.).

Unguentum Belladonnæ (10 per cent).

Belladonnæ Radix, the root of Atropa belladonna, containing 0.45 per cent of alkaloids.

Emplastrum Belladonnæ. The belladonna plaster mass must yield between 0.25 and 0.30 per cent of the alkaloids of belladonna.

Hyoscyamus. The leaves of Hyoscyamus niger (henbane) yield not less than 0.040 per cent of alkaloids. Dose, 0.2 gram.

Extractum Hyoscyami (0.15 per cent of alkaloids). Dose, 50 mg.

Tinctura Hyoscyami (0.004 per cent of alkaloids). Dose, 2 cc.

Stramonium, the dried leaves and flowering tops of Datura stramonium, containing 0.30 per cent of alkaloids.

Extractum Stramonii (1.2 per cent of alkaloids). Dose, 20 mg.

Tinctura Stramonii (0.03 per cent of alkaloids). Dose, 0.75 cc. (12 min.).

B. P.

Belladonnæ Herba, belladonnæ folium; belladonna herb, belladonna leaf, the leaves and tops of Atropa belladonna, containing 0.3 per cent of alkaloids.

Belladonna Pulverata, powdered belladonna leaf adjusted to contain 0.3 per cent of alkaloids, calculated as hyoscyamine. Dose, 0.03 to 0.2 gram ($\frac{1}{2}$ to 3 gr.).

Extractum Belladonnæ Herbæ Liquidum, liquid extract of belladonna herb. Dose, 0.015 to 0.06 mil.

Extractum Belladonnæ Siccum (1 per cent of alkaloids). Dose, 0.015 to 0.06 gram ($\frac{1}{4}$ to 1 gr.).

Tinctura Belladonnæ (0.03 per cent of alkaloids). Dose, 0.03 to 2 mil. (5 to 30 min.).

Belladonnæ Radix, the dried root of Atropa belladonna. Dose, 0.03 to 0.12 gram.

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EXTRACTUM BELLADONNÆ LIQUIDUM (0.75 per cent of alkaloids). Dose, 0.015 to 0.06 mil. ($\frac{1}{4}$ to 1 min.).

EMPLASTRUM BELLADONNÆ (0.25 per cent of alkaloids).

LINIMENTUM BELLADONNÆ (0.375 per cent of alkaloids).

HYOSCYAMUS, the dried leaves and flowering tops of Hyoscyamus niger, henbane.

EXTRACTUM HYOSCYAMI SICCUM (0.3 per cent alkaloids). Dose, 0.016 to 0.06 gram ($\frac{1}{4}$ to 1 gr.).

TINCTURA HYOSCYAMI (0.005 per cent of alkaloids). Dose, 2 to 4 mil. (30 to 60 min.).

EXTRACTUM HYOSCYAMI LIQUIDUM (0.05 per cent of alkaloids). Dose, 0.2 to 0.4 mil. (3 to 6 min.).

STRAMONIUM (0.25 per cent of alkaloids). Dose, 0.03 to 0.2 gram ($\frac{1}{2}$ to 3 gr.).

EXTRACTUM STRAMONII LIQUIDUM, liquid extract of stramonium. Dose, 0.03 to 0.2 mil.

EXTRACTUM STRAMONII SICCUM, dry extract of stramonium. Dose, 0.015 to 0.06 gram; in post-encephalitic and similar conditions, 0.06 to 0.5 gram.

TINCTURA STRAMONII (0.025 per cent of alkaloids). Dose, 0.3 to 2 mil. (5 to 30 min.).

Alkaloids

ATROPINA (U. S. P., B. P.). An alkaloid usually obtained from Atropa Belladonna and from species of Datura and Hyoscyamus, or produced synthetically.

ATROPINÆ SULFAS (U. S. P.), Atropinæ sulphas (B. P.), a white crystalline powder, with a very bitter taste, soluble in water and alcohol. Dose, U. S. P., 0.5 mg.; B. P., 0.25 to 1 mg.

LAMELLA ATROPINÆ (B. P.), gelatin discs, each containing $\frac{1}{5000}$ gr. of atropine sulfate.

OCULENTUM ATROPINÆ (B. P.) (0.25 per cent).

TABELLÆ ATROPINÆ SULPHATIS (B. P.), tablets of atropine sulphate. Dose, 0.00025 to 0.001 gram.

HYOSCINÆ HYDROBROMIDUM (B. P.), SCOPOLAMINÆ HYDROBROMIDUM (U. S. P.) ($C_{17}H_{21}NO_4HBr, 3H_2O$), the hydrobromide of hyoscine or scopolamine. It is obtained from hyoscyamus, scopola and other Solanaceæ, and forms colorless, transparent crystals with an acrid, bitter taste, and is very soluble in water, less so in alcohol. Dose, U. S. P., 0.5 mg.; B. P., 0.0003 to 0.0006 gram.

HOMATROPINÆ HYDROBROMIDUM (U. S. P., B. P.) ($C_{16}H_{21}NO_3HBr$), the hydrobromide of an alkaloid prepared from tropine by condensation with mandelic (oxytoluic) acid, a white crystalline powder soluble in 6 parts of cold water. Dose, B. P., 0.001 to 0.002 gram ($\frac{1}{64}$ to $\frac{1}{32}$ gr.).

LAMELLA HOMATROPINÆ (B. P.), gelatin discs, each weighing $\frac{1}{50}$ gr. and containing $\frac{1}{100}$ gr. of homatropine hydrobromide.

EUCATROPINÆ HYDROCHLORIDUM (U. S. P.), $C_{17}H_{25}O_3N.HCl$, a white powder, very soluble in water.

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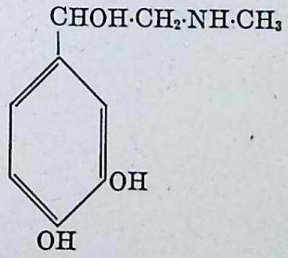
IV. STIMULANTS OF SYMPATHETIC ACTIVITY

SYMPATHOMIMETIC DRUGS

1. Epinephrine (Adrenaline)

The suprarenal glands of all vertebrates contain a body which possesses a powerful action on the organism, and which the glands normally secrete in the blood stream. The active principle in the form of a benzoyl compound was first isolated by Abel and named *epinephrine*, but as a pure crystalline compound it was first isolated in 1901 by Takamine and by Aldrich and named *adrenalin*. It is also known under the trade names of *adrenine*, *suprarenine*, etc.



Epinephrine

Epinephrine has also been found in the external neck glands of certain toads. It is a feebly basic compound having the structure shown and may be designated as 3, 4 dioxyphenyl ethanol methylamine. Epinephrine is also prepared synthetically, and a number of other amine compounds similar to it in structure have proved to resemble it also in action in many features; other amines less closely related chemically tend to depart further from the typical epinephrine action (Barger and Dale). Epinephrine is levorotary to polarized light; the dextrorotary isomer has only about one-twelfth of the activity of the natural substance (*cf.* Atropine and Scopolamine).

The characteristic action of epinephrine is best elicited by its injection into a vein, when it induces effects which are thus for the most part identical with those of stimulation of the sympathetic nerves. The group of amines of which it is the best known member have therefore been termed the sympathomimetic amines. The symptoms show certain analogies with those induced by nicotine, but the latter affects a wider

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area from its involving the parasympathetic autonomic nerves as well as those of the true sympathetic. And the point at which nicotine acts is the ganglion cell, while epinephrine involves the other end of the peripheral neuron. It should be added that some of the sympathetic terminations are not involved in the action of epinephrine; the secretory fibers in the sweat glands are not affected, for example, although they are of sympathetic origin.

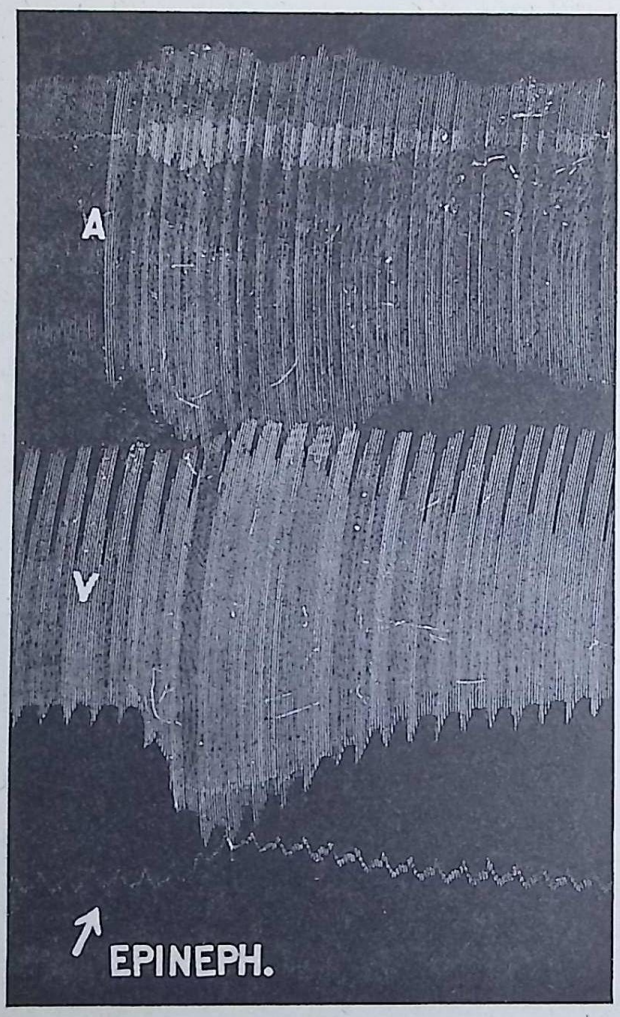

FIG. 40.—Effect of very small dose of epinephrine upon the dog's heart and blood-pressure. *A*, Auricle; *V*, ventricle. Lever moves down in systole. Lower tracing. Blood-pressure. The very small dose gives almost pure muscular action with practically no vagus effect.

Circulation.—On the intravenous injection of epinephrine a very marked rise in the arterial blood-pressure occurs, accompanied at first by acceleration, then by slowing, and later again by acceleration of the heart. This rise in blood-pressure is due to constriction of the vessels of the abdominal cavity, accompanied by an increase in the output of the heart. The sudden increase in pressure occurs after destruction of the vasomotor center and cord, or after section of the splanchnic nerves

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and paralysis of the ganglia on the vasoconstrictor nerves, so that it is obviously due to direct action on the muscle of the vessel walls, or on the terminations of the nerves in them. The greatest constriction is seen in the vessels of the splanchnic area, but most of the other vessels are also involved in lesser degree. Thus the limb vessels are narrowed less than those of the intestine, and the pulmonary and cranial arterioles are so slightly constricted that there has been some difficulty in proving that they are involved in the general action; most observers now hold that there is narrowing in these regions also. The effect on the coronary artery of the heart has also been the subject of dispute, most investigators finding that it is dilated by epinephrine; but though this is often the prevailing effect, very small concentrations of epinephrine cause distinct contraction of the coronary artery and slow the passage of blood through the heart in the anesthetized animal with the chest open. However, observations made upon the unanesthetized dog by means of a thermostromuhr placed upon the circumflex branch of the coronary artery showed that the intravenous injection of 0.05 to 0.1 cc. of a 1 to 1,000 solution of epinephrine causes an immediate but transient increase in coronary blood flow. This increase which may be as great as from two to four times the control value lasts for about seven minutes.

In organs in which the vessels are obviously constricted, the degree varies considerably, apparently according to the amount of control normally exercised by the constrictor nerves; thus the vessels of the uterus are more contracted than those of the bladder, and these again more than those of the striated muscles, which may even be dilated from the high blood-pressure arising from the constriction of the splanchnic vessels (Fig. 42). The smaller veins are constricted as well as the arterioles, and the constriction of the hepatic venules is more marked than that of the portal branches so that the blood accumulates in the liver, which becomes greatly swollen. This leads to a large escape of plasma from the blood and blood-counts therefore show an unusually high content of red cells.

After moderate quantities of epinephrine the blood-pressure falls again after about five minutes, and not infrequently descends below the normal level. And in some instances when epinephrine is injected into an animal whose blood-pressure is very high, a fall of pressure occurs instead of the usual rise. Further, when the sympathetic myoneural junctions in the vessels have been paralyzed by ergotoxine, epinephrine causes a distinct fall in the blood-pressure instead of the usual rise (see Fig. 44, p. 510). This reversal of the epinephrine reaction was formerly explained by the theory that it stimulates not only the terminations of the vasoconstrictor nerves but also those of the vasodilators, and that the former usually prevail, but under certain conditions they may be exhausted more quickly or may be ineffective and the vasodilator stimulation then prevails. However, as shown by Dale and Richards, epinephrine causes dilation of the capillaries. This results in a decrease in the peripheral resistance which would lead to a fall in blood-pressure were it not compensated for by the constriction of the arterioles and the increased cardiac output. If the heart does not

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respond by an increased output and the constriction of the arterioles fails to occur, or is of short duration, a fall in blood-pressure results.

When epinephrine solutions are injected into the femoral artery of a dog the usual response is a combined constriction and dilatation, the two phases varying in their time relationships (Roome). The site of dilatation is the capillaries while the constriction is confined to the arteries and arterioles.

When very minute quantities of epinephrine are injected into an anesthetized cat or dog, a fall in the blood-pressure generally occurs, while a larger quantity induces vasoconstriction with the typical rise in pressure. In the unanesthetized animal a fall in blood-pressure does not occur when epinephrine is given intravenously, any effective quantity inducing always a rise in pressure.

The acceleration of the heart under epinephrine is due to stimulation of the terminations of the accelerator nerves in the heart-muscle, and is therefore accompanied by a stronger contraction and more complete evacuation of the chambers; if the dose injected be large the accelerator action is too great to admit of complete relaxation during the diastole, and the output of the heart may be smaller, and a drop in the blood-pressure is observed. This accelerated beat is the characteristic feature of the epinephrine action, but it often gives place to the slow, full beat characteristic of inhibitory activity. This second phase of slowing of the heart beat is not observed if the vagi are divided or if atropine is given before epinephrine, so that it obviously arises from excitation of the vagus center; this is not entirely a direct epinephrine action but is largely a secondary result of the high blood-pressure, which induces congestion of the brain and arouses the vagus center to activity. After a short time, the blood-pressure beginning to fall, or, the vagus center becoming exhausted, the accelerator stimulation again gains the upper hand and the pulse is again much accelerated.

The effect of epinephrine on the mammalian heart is thus in small doses to accelerate and strengthen it; in large amounts the acceleration may be excessive and impair its efficiency, or the acceleration may be temporarily replaced by inhibition which also reduces the output. Epinephrine increases the irritability of the heart and thus predisposes it to pass into fibrillary contractions. The frog's heart is less easily affected than that of the mammals, but similar changes have been observed.

In man, the subcutaneous injection of 0.5 to 1 mg. of epinephrine causes an elevation of blood-pressure, pallor of the face and extremities and an accelerated pulse rate. The systolic blood-pressure rises about 10 to 30 mm. of mercury reaching its maximum in about one-half hour and subsiding after one to two hours. The diastolic pressure usually drops slightly indicating a diminished peripheral resistance. The pulse rate is increased 10 to 20 beats per minute. The cardiac output may be increased by 75 per cent above its basal level.

The action on the heart may be demonstrated by perfusing very dilute solutions of epinephrine through the vessels of the excised heart, and the same method is used in investigating its action on the vessels of other organs. In the excised heart the accelerator and augmentor

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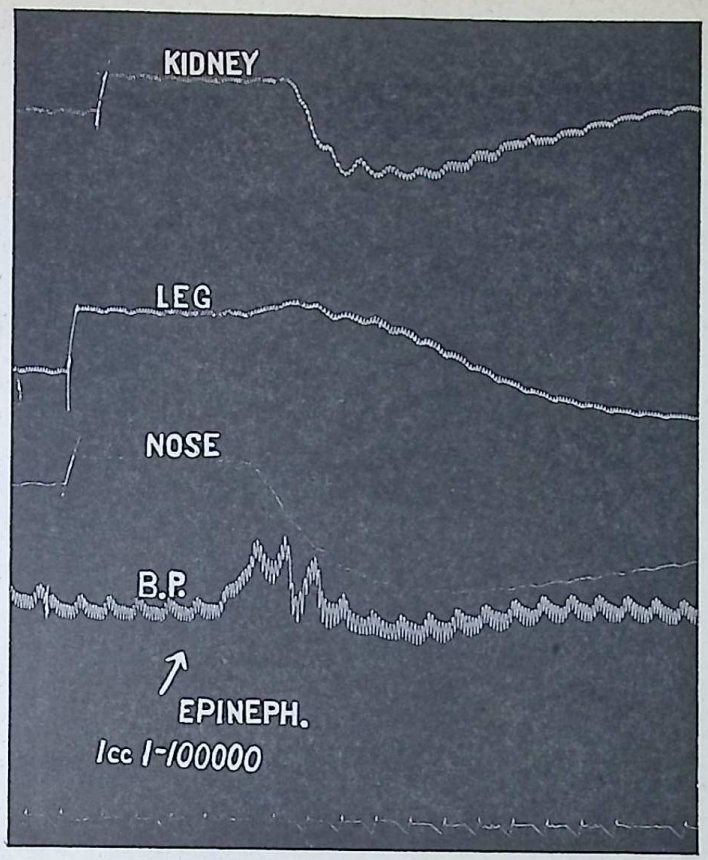

FIG. 41.—Change in distribution of blood in dog from small dose of epinephrine. With the increase in blood-pressure there is marked decrease in volume of kidney from constriction of its vessels. There is also constriction of vessels in mucous membrane of the nasal cavity. At first there is a passive dilatation of the leg vessels as blood is diverted to muscles from the splanchnic area, and as blood-pressure returns to normal the leg volume decreases (Nelson).

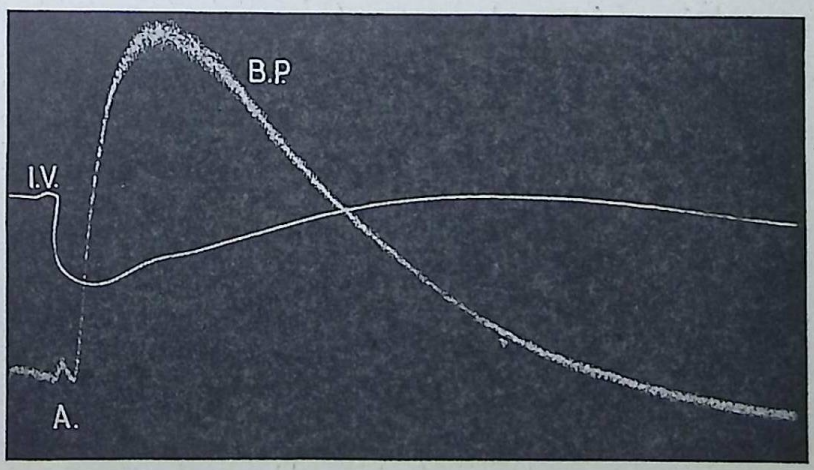

FIG. 42.—Blood-pressure (*B.P.*) and bowel volume (*I.V.*) of cat. At *A* injection of epinephrine. The blood-pressure rises and bowel volume diminishes, indicating constriction of the mesenteric vessels. As these relax again the blood-pressure falls. The vagi had been divided previously, so that there is no secondary slowing of the heart. (See also Fig. 41.)

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action alone is visible, the stage of slowing being absent. The contraction of the vessels in such organs as the kidney is shown by the diminished outflow from the veins when epinephrine is added to the perfusing fluid; and different organs respond in different degrees, little retardation of the flow occurring in the lungs, brain and heart compared with that in the intestines, limbs, and kidney. A similar constriction of the vessels may be observed when a solution of epinephrine is applied to a mucous membrane, for the part becomes pale and anemic from the constriction of the vessels; this is well seen when the drug is applied to the congested conjunctiva or to the mesentery. Painted on the unbroken skin epinephrine has no effect, as it fails to penetrate it, but denuded surfaces become blanched, and hemorrhage ceases from small vessels.

When it is injected hypodermically, the skin and subcutaneous tissues around the point of injection become pale and anemic and may be cut into without bleeding, and when it is applied to a bleeding surface, the hemorrhage is arrested unless some large artery has been opened. But even the direct application of epinephrine to a lesion of the lung or brain has little effect in stopping the bleeding, the vessels in these organs not being constricted by epinephrine to the same extent as those of other organs.

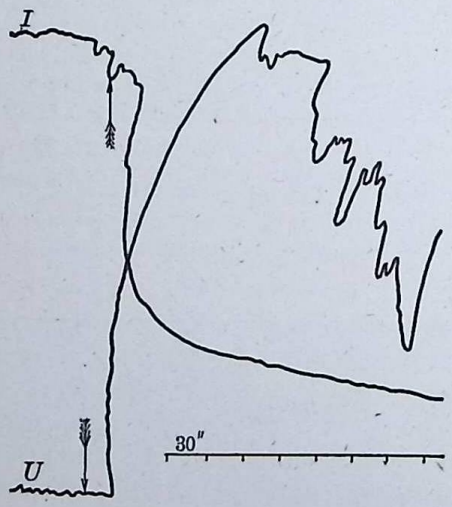

FIG. 43.—Tracing of the movements of intestine (*I*) and of the uterus (*U*) of a rabbit under epinephrine injected at the point marked with an arrow. The intestine relaxes while the uterus contracts powerfully.

The **Respiration** sometimes becomes irregular during the period of high blood-pressure, and periods of strong and rapid breathing may alternate with apnea. Small doses increase the depth of respiration, while larger doses reduce it. These effects are independent of the blood-pressure changes and are not affected by vagotomy. Perfusion experiments indicate that epinephrine acts directly on the respiratory center. However, the apnea observed following its injection is a reflex effect initiated by the elevated blood-pressure in the carotid sinus.

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Stomach and Intestine.—The intravenous injection of epinephrine is followed by immediate cessation of the movements of the stomach and intestine, which become relaxed to their full extent. This is in accordance with their innervation, for the splanchnic fibers are the inhibitory nerves of those organs and their stimulation also arrests peristalsis and causes relaxation (Fig. 43). But certain specialized parts of the bowel wall receive motor fibers from the sympathetic—the pyloric, ileo-colic and internal anal sphincters and the muscularis mucosa—and these are thrown into contraction by epinephrine. The movements of the gall-bladder are inhibited and those of the bile-duct are increased by sympathetic stimulation and also by epinephrine.

The reaction of the **Bladder** to epinephrine differs in different species of animals according to the nature of the dominant impulses of the lumbar sympathetic nerves.

Uterus.—The reaction of the uterus to epinephrine differs in different animals and even in the same animal at different periods. In the non-pregnant cat, epinephrine generally causes inhibition of the movements and relaxation, while in the pregnant cat its injection is followed by powerful contractions; in the rabbit epinephrine almost always causes contraction whether the animal is gravid or not, while in the dog the uterus first contracts and then passes into a position of relaxation and inhibition. In each case the action of epinephrine is identical with that of stimulation of the hypogastric nerves which carry both motor and inhibitory fibers to the uterus; the relative power of the two sets of fibers varies in different animals and in different conditions in the same way as the action of epinephrine (Fig. 43). Small doses of epinephrine reduce the amplitude of the contractions of the human gravid uterus. However, after larger doses uterine activity is markedly increased and then inhibited.

The Eye.—The intravenous injection of epinephrine is followed by dilatation of the pupil, the eyelids are widely opened, the eyeball is protruded, and the nictitating membrane withdrawn; the action corresponds exactly to the effects of stimulation of the cervical sympathetic fibers; it occurs when these have been cut, and is even intensified when they have been allowed to degenerate. Applied locally to the eye, it constricts the vessels of the conjunctiva and often dilates the pupil and reduces the intra-ocular tension for a short time.

Bronchial Muscle.—Epinephrine injected intravenously dilates the bronchi widely, an effect which is especially noticeable when they have been previously constricted by pilocarpine or physostigmine. In bronchial asthma the subcutaneous injection of small doses of a 1 to 1000 solution of epinephrine (0.2 to 0.5 cc.) will usually give relief through its relaxing effect upon the bronchial musculature. This action is not the same as the dilation caused by atropine, but arises from epinephrine stimulating the terminations of the bronchial sympathetic fibers, which cause relaxation of the muscle.

Other Organs containing unstriated muscle are similarly affected, some undergoing contraction, while others are inhibited under epinephrine, and in each case the result corresponds with the effect of stimulation of

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the fibers of the sympathetic supply. The spleen reacts to even minute doses of epinephrine with contraction. Epinephrine induces contraction of the pigment in the scales of the small fish, *fundulus* and of the melanophores of the frog.

The **Secretions** do not present such marked changes under epinephrine, though they are also generally increased when they are controlled by the sympathetic nerves. This is due to the fact that the blood supply is simultaneously reduced by the vasoconstriction. For example, the secretion of the pancreas is arrested by epinephrine as a result of the ischemia of the gland which the drug induces. The saliva under epinephrine corresponds in character with that secreted on stimulation of the cervical sympathetic trunk, not with that from stimulation of the chorda tympani, which is a cranial autonomic nerve and is therefore not susceptible to epinephrine.

The **sweat glands** provide the most notable exception to the rule that epinephrine has the same effect as sympathetic stimulation, for though they are innervated by sympathetic fibers whose stimulation causes secretion, epinephrine has no effect on the sweat secretion. Although belonging to the sympathetic system, anatomically, the innervation of the sweat glands acts pharmacologically as if a part of the parasympathetic. In other words, the postganglionic sympathetic fibers innervating the sweat glands are cholinergic releasing acetylcholine as their chemical mediator. As cholinergic fibers they are paralyzed by atropine (*cf.* page 468). The sympathetic preganglionic fibers and the postganglionic sympathetic fibers which cause vasodilation are also cholinergic and hence insofar as their pharmacological reactions are concerned do not react like the rest of the anatomic sympathetic system.

The secretion of the **urine** is often arrested immediately on the injection of epinephrine and is then considerably augmented. This appears to be due to the vascular action, the renal vessels being constricted at first but relaxing sooner than those of the other organs; the flow of blood through the kidney is thus reduced at first and the urinary secretion falls or stops altogether; then an abnormally large flow occurs from the renal vessels dilating while the blood-pressure is still high, and more urine is accordingly secreted.

The **basal metabolic rate** is elevated following the injection of epinephrine with an increase in the utilization of carbohydrate and a slight rise in body temperature. Glycogenolysis in the liver is stimulated with an increase in the level of the blood sugar which may give rise to glycosuria. In fasting animals hyperglycemia occurs with a concurrent storage of glycogen in the liver so that the effect of epinephrine on carbohydrate metabolism is not limited to its glycolytic action. The accelerated breaking down of glycogen arises from epinephrine stimulating the terminal mechanism of the sympathetic nerves in the liver that control the glycogenic function. However, epinephrine also stimulates glycogenolysis in the muscles with the formation of lactic acid which is converted to glycogen in the liver. The urea excretion is lessened during the stage of diminished urinary flow but during the stage of

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polyuria it is increased, the urea and also the chloride excretion rates varying directly with the rate of excretion of water.

Mechanism of Action.—Epinephrine thus acts in the same way as stimulation of the sympathetic nerves and is held to induce its effects by stimulating the mechanism lying between the nerves and the muscle. It obviously does not act on the contractile muscle itself, for some involuntary muscle contracts under it while in other organs it relaxes. And it is found that after ergotoxine, an alkaloid which antagonizes the action of epinephrine in some organs, the muscle remains active though the receptor on which epinephrine acts is paralyzed. Epinephrine therefore does not act on the contractile mechanism of muscle. On the other hand it does not act on the anatomical nerve ends, for after these have degenerated and disappeared, the usual effects of epinephrine are elicited by its injection. It is obvious that the action is exercised on some substance intermediate between the nerve and the contractile material of muscle and this has been termed the "myoneural junction or receptive substance."

Epinephrine injected intravenously acts in very small quantities, 0.001 mg. often sufficing to raise the blood-pressure in the dog. The effect is of very short duration, but it may be repeated indefinitely by fresh injections. There is a rapid inactivation of epinephrine in the tissues. When the blood-pressure regains its normal level after an injection of epinephrine, none of the alkaloid can be detected in the blood or tissues. Since epinephrine is readily oxidized *in vitro* by reduced cytochrome C, it was formerly believed that a similar oxidation occurred in the body and that epinephrine was inactivated in this way. However, recent evidence indicates that epinephrine is excreted in the form of a conjugated compound in which sulfuric acid is combined with one of the phenolic hydroxyl groups (Beyer and Shapiro).

Epinephrine applied **locally** induces such vasoconstriction that it is only slowly absorbed. Injected hypodermically it causes local ischemia so that comparatively large doses (0.5 to 1 mg.) compared with those necessary by intravenous injection are required to give a distinct rise of blood-pressure and dilation of the bronchi; injected intramuscularly it induces stronger general effects. Epinephrine is ineffective when administered orally unless used in large doses (4 mg.) being converted in the gastro-intestinal tract to toxic oxidation products. The massage of the skin over the area in which a hypodermic injection has been made enhances the effect of the drug, the action of which may be elicited in this way even an hour after its original injection.

Toxicology.—Animals are poisoned by large amounts injected hypodermically with prostration, collapse and paralysis of the central nervous system, ending in failure of the respiration and edema of the lungs. Similar symptoms arise from the intravenous injection of very large doses, but here the effects of the high blood-pressure are also in evidence in numerous hemorrhages. The minimal lethal dose of epinephrine administered subcutaneously to man is about 10 mg. per kilo of body weight, but alarming symptoms may follow the intravenous injection of a total dose as little as 0.3 mg. Atropine is a useful antidote.

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Adrenergic Action.—Cannon and his co-workers first demonstrated that the stimulation of a sympathetic nerve in an intact animal will release into the blood stream a substance having many of the characteristics of epinephrine and to this substance they gave the name *sympathin.* While epinephrine and sympathin have similar actions in many instances, they show certain differences in action which should preclude their identity. One of these differences is in their relation to ergotoxine which produces the well-known vasomotor reversal effects with epinephrine, but with sympathin there is no such phenomenon. Moreover, whereas epinephrine exerts both excitatory as well as inhibitory effects, this is not the case with sympathin. In fact the sympathins derived from the stimulation of different sympathetic nerves, such as those going to the heart or liver, or from stimulation of the hypogastric nerve differ, not only from epinephrine, but also from each other. On this account, the sympathins have been put into two groups—sympathin E and sympathin I, depending upon whether they stimulate the structure to which the nerve is distributed or depress it. Sympathin E is liberated by nerve endings in structures which are excited by sympathetic stimulation, *e. g.*, the cardiac muscle, liver, blood-vessels, smooth muscle of the skin, etc. Sympathin I, is liberated by nerve endings in structures which are inhibited by sympathetic stimulation, *e. g.*, the intestinal musculature, the coronary vessels of the heart, etc.

It is now believed that the sympathin is released in the immediate vicinity of the reacting mechanism and probably within the cell itself and that this production of sympathin is responsible for the transmission of the sympathetic nerve impulse to the affected mechanism. The fibers which liberate these epinephrine (adrenalin)-like substances are therefore designated as **adrenergic.** They include the sympathetic endings of the smooth muscle in the skin, the gastro-intestinal tract, the cardio-accelerator apparatus, the vasoconstrictors, the hepatic nerves, the hypogastric, etc. Epinephrine, then may be said to simulate the effect of stimulating adrenergic fibers. It includes the effects elicited by the liberation of both sympathin E and I. The action of both sympathins and epinephrine are augmented by cocaine and both give the Viale color reaction but as already stated the two are not identical.

Therapeutic Uses.—Epinephrine hydrochloride is extensively used in therapeutics in the form of a 1 to 1,000 aqueous solution with the addition of chlorobutanol and potassium bisulfite as stabilizing agents. It is also available as a 1 to 10,000 and 1 to 2,600 solution for injection, in the form of an inhalant (1 to 1,000) with chloretone, as a suppository, as an ointment, as a 1 to 100 solution for use as a spray, and as 1 to 500 suspension in oil. Epinephrine is prepared from adrenal glands or synthetically. The latter preparations are marketed in the form of the levorotatory isomer which is identical with the naturally occurring compound, the dextrorotatory isomer being relatively inactive.

The principal uses of epinephrine depend upon its action in constricting the blood-vessels of the skin, stimulating the heart, relaxing the bronchioles and inducing glycogenolysis.

The general action of epinephrine on the circulation may be induced

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in such emergencies as heart failure, in which its powers of restoring the circulation have been proved both in animals and in man; for example, in animals in which the heart has been arrested by excessive doses of ether, the circulation may be restored by the intravenous or intracardiac injection of epinephrine. The dose suggested for intravenous injection is 0.2 cc. of the solution well diluted. Excessive doses may be harmful. In this connection it is to be borne in mind that epinephrine may tend to cause fibrillation of the ventricle in cyclopropane and chloroform anesthesia. The intracardiac injection of epinephrine has been frequently carried out with success in cases in which the heart has stopped beating as in shock, anesthesia, electrocution, drowning and suffocation. When used in these cases the drug should be injected directly into the cardiac musculature through a long needle inserted in the fourth left intercostal space.

Epinephrine has also been employed in "shock" to constrict the vessels. Where the symptoms are largely nervous in origin, this may be good practice, but when true secondary shock has developed with capillary distention and reduced blood volume, epinephrine is of no service and indeed it may be harmful if large doses are used. The treatment should aim at increasing the volume of the blood in circulation by the transfusion of blood or the infusion of saline or glucose solution.

The great use of epinephrine is, however, due to its local effects on the vessels. No other body is known which induces such complete contraction of the vessels in any part to which it is applied, and in addition it has practically only local effects, unless it is injected into the blood. Complete bloodlessness of a part may thus be elicited without significant alteration of the general blood-pressure, and in fact without any appreciable effect upon other parts of the body. This local ischemia has been largely employed to allow of bloodless operations on the eye and to remove congestion of the conjunctiva from various causes. It is often administered with the local anesthetics in operations on the eye, being used especially with cocaine and procaine. Here it not only gives a bloodless field of operation but also limits the absorption of the anesthetic and prolongs its action. In congestion of the nasal mucous membrane and in operations on the nose it is also used extensively and with much success; the 1 per mille solution may be sprayed into the nose, or cotton soaked in it may be packed into the cavity. In epistaxis and in operations on the nose or throat, the hemorrhage ceases almost completely and the contraction of the mucous membrane permits of a clearer view of the field of operation. Hay fever is often temporarily relieved by similar treatment.

The constriction of the vessels in a part to which epinephrine is applied retards the absorption of local anesthetics injected with the epinephrine, and at the same time permits of their exercising a more marked local effect. This fact is utilized in surgery to prevent the absorption of the local anesthetics and to intensify their action.

The hypodermic injection of 0.3 to 0.5 cc. of the solution often gives relief in asthmatic attacks immediately; apparently enough of this

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large dose is absorbed to stimulate the dilator nerve fibers in the bronchi. The dose may be repeated in fifteen minutes if required but the effect usually lasts much longer than that. It is most valuable in the treatment of a severe acute attack, other drugs being preferred when the asthmatic paroxysms are frequent. For use in asthma, epinephrine is usually administered hypodermically in the form of a 1 : 1,000 solution. It is also available in the form of a 1 per cent solution to be used as a spray. When used in this concentration a sufficient amount of the drug is absorbed through the mucosa to induce the desired affect. The suspension of epinephrine in oil (1 to 500) is also used to prolong the action of the drug and to maintain sustained relief for a longer period than is possible when the aqueous solution is administered. The dose of the suspension in oil is 0.2 to 1.5 cc. (0.4 to 3 mg.) administered intramuscularly every eight to sixteen hours.

In urticaria, angioneurotic edema, and serum sickness the drug may be given hypodermically in doses of 0.6 to 1 cc. of the 1 to 1,000 solution and it often produces a great improvement in the symptoms.

Epinephrine may also be used in the same manner and dosage to prevent the occurrence of the nitritoid crises following the use of arsphenamine or indeed to treat this condition in case it has occurred. Also 0.5 to 1 cc. of the solution may be injected subcutaneously to offset the symptoms of hypoglycemia produced at times in a diabetic patient by insulin. Its effectiveness in relieving hypoglycemia is dependent upon the presence of glycogen in the liver. If the supply of glycogen is depleted as, for example, following muscular exertion the injection of epinephrine is without effect on the level of the blood sugar.

Epinephrine has also been used locally in the form of a 2 per cent solution in the treatment of glaucoma. Although favorable results are obtained in some cases, it is ineffective in others.

Preparations

U. S. P.

Epinephrina, *l*-methylaminoethanolcatechol.

Liquor Epinephrinæ Hydrochloridi, 0.1 of 1 per cent solution of epinephrine hydrochloride. Dose, 0.5 cc.

Injectio Epinephrinæ Hydrochloridi. Dose, 1 mg., subcutaneously or intramuscularly.

Nebula Epinephrinæ Hydrochloridi, epinephrine hydrochloride spray (1 per cent).

B. P.

Adrenalina, epinephrine. Dose, 0.0001 to 0.0005 gram.

Liquor Adrenalinæ Hydrochloridi, 0.1 of 1 per cent solution of adrenaline hydrochloride. Dose, 0.12 to 0.5 mil.

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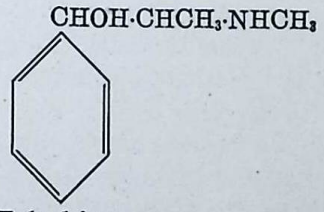
2. Ephedrine

Ephedrine is an alkaloid obtained from ma huang (Ephedra equisetina), a drug which has been used by the Chinese from early times. The alkaloid, which was first isolated by Nagai in 1887, is closely related both chemically and pharmacologically to epinephrine as will be seen by the following formula:



Ephedrine

Ephedrine remained practically unnoticed until 1923 when Schmidt and Chen undertook its systematic pharmacologic investigation and demonstrated its epinephrine-like action.

Solutions of ephedrine are more stable than are those of epinephrine and the drug is active when given by mouth.

Actions.—In man the drug in doses of from 20 to 50 mg. given by mouth produces an increase in blood-pressure with decreased heart rate, associated at times with some throbbing in the head and a feeling of palpitation and anxiety. These effects may last for two hours. In certain persons the anxiety complex is so marked as to serve as a contra-indication to the use of the drug.

Injected into animals the alkaloid produces an increase in heart rate and in the strength of the contractions and a prolonged rise in blood-pressure. Repeated injections result in less and less response in which respect ephedrine differs from epinephrine which does not show this

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phenomenon of tachyphylaxis. The increase in the rate of the heart is due to an action upon the accelerator mechanism, but in man this action may be overcome by increased activity of the inhibitory mechanism, and slowing of the heart often results together with an increase in both systolic and diastolic pressure. In the unanesthetized dog small doses of ephedrine induce at once a marked bradycardia followed by extrasystoles and a slow rhythm (Meek and Seevers). These two stages are the result of a primary followed by a reflex stimulation of the vagus nerve, the reflex action on the vagus being the result of increased blood-pressure. Tachycardia follows the stage of slowing and in case atropine is given at the beginning of the observations the tachycardia comes on early. These cardiac phenomena are largely prevented or removed by the administration of sodium barbital, which acts to lessen the vagal effects by a certain degree of paralysis and also probably by some depression of the automatic centers.

In animals vasoconstriction occurs, especially in the splanchnic area, resembling that produced by epinephrine except that it is more prolonged. Inhibition of the intestine has been reported by some workers, but the effect of ephedrine on the gastro-intestinal tract is not striking. Contraction of the uterus is produced in all species of animals examined. Upon the normal bronchial muscles there is little effect, but relaxation follows if the tone of the muscles has been increased by histamine or by physostigmine. The pupil is dilated due to an action upon the iris and occurring after the iris has been denervated by section of the cervical sympathetics, and when cocaine is no longer active, it must act peripherally to the latter drug.

Ephedrine like epinephrine has an excitatory action on the central nervous system as shown by the shortening of the period of the hypnotic action of the barbiturates. The drug also stimulates mildly the respiratory center.

The alkaloid has little effect upon secretions such as the sweat, nor does it alter body temperature, although it was for these two effects that it has been employed by the Chinese for so long.

The fate of ephedrine in the body is unknown. It has a relatively low toxicity.

Mechanism of Action.—The drug resembles epinephrine closely in its effect and in general acts upon the same structures in the body. However, in addition to its sympathomimetic action, as with epinephrine, it also acts upon the muscle cell itself.

It has been suggested that ephedrine manifests an action in relation to epinephrine similar to that which exists between physostigmine and acetylcholine (Gaddum). In the latter case, as was discussed under the general subject of physostigmine, this drug was shown to inhibit the action of the enzyme which is responsible for the rapid destruction of the acetylcholine which is liberated when parasympathetic (cholinergic) nerves are stimulated. In like manner when sympathetic (adrenergic) nerves are stimulated, ephedrine which is closely related chemically to epinephrine, may inhibit the destruction of epinephrine in the same manner that physostigmine protects acetylcholine, and in this way

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certain of the ephedrine actions may really be due to epinephrine. The action of epinephrine is definitely potentiated by ephedrine when the ephedrine is in low concentration, but it is antagonized by high concentrations. This latter effect is explained by the theory that the ephedrine combines and blocks the motor receptors. Since ephedrine resembles epinephrine closely in structure, it is logical to expect that it too should exert an adrenergic action.

From the clinical standpoint the main difference in its action from that of epinephrine is that ephedrine is active when given by mouth and its effects are more prolonged than are those of epinephrine.

Therapeutic Uses.—Ephedrine in the form of its salts is widely used in medicine particularly for the symptomatic relief of asthma and other allergic disorders. It is derived from natural sources or prepared synthetically. The latter preparation is racemic and is designated as **racéphedrine.**

Ephedrine preparations are used locally in the eye to dilate the pupils and in the nostrils to shrink the congested mucosa in rhinitis and sinusitis. For the latter purpose it is used in a 0.5 to 2 per cent solution or in the form of a jelly. In ophthalmologic work, a 4 per cent solution is used.

Ephedrine is useful in asthma especially to prevent the attacks but it often fails to elicit the desired response. For this purpose it may be given orally in doses of 20 to 50 mg. every three to four hours. It seems to be more active in preventing an attack than in relieving one already present. It is also used in hay fever and urticaria, usually in the form of a spray or in solution.

Ephedrine is used to counteract the low blood-pressure sometimes seen in spinal anesthesia but it is of doubtful value in serious circulatory collapse. Ephedrine has been found useful as an adjunct in the symptomatic treatment of some cases of myasthenia gravis. It has also been recommended in the management of enuresis. The administration of ephedrine tends to produce symptoms of anxiety which may constitute a contraindication to its use. For this reason it is often administered in combination with one of the barbiturates.

Preparations

U. S. P.

Ephedrina, ephedrine $C_{10}H_{15}ON$. An alkaloid derived from various species of ephedra. It is soluble in water, alcohol, and liquid petrolatum.

Ephedrinæ Hydrochloridum. The hydrochloride of ephedrine is soluble in water and in alcohol. Dose, 25 mg.

Ephedrinæ Sulfas. The sulfate of ephedrine is soluble in water and with difficulty in cold alcohol—more freely in hot alcohol. Dose, 25 mg.

B. P.

Ephedrina, ephedrine, the hemihydrate of *l*-α-hydroxy-β-methylaminopropylbenzene. Dose, 0.016 to 0.1 gram.

Ephedrinæ Hydrochloridum. Dose, 0.016 to 0.1 gram.

Tabellæ Ephedrinæ Hydrochloridi, tablets of ephedrine hydrochloride. Dose, 0.016 to 0.1 gram.

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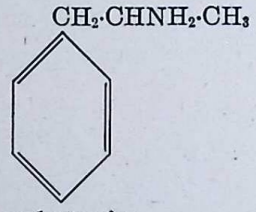
3. Amphetamine

Amphetamine (benzedrine) 1-phenyl-2-aminopropane, is a synthetic preparation belonging to the sympathomimetic group of drugs and closely related to epinephrine and ephedrine. It is a colorless liquid which on exposure to air rapidly changes into the carbonate, both the base itself and the carbonate being volatile. The free base is administered by inhalation or as a spray in the form of a 1 per cent solution in liquid petrolatum. The sulfate of benzedrine, on the other hand, is non-volatile and is used for both local and general effects in the form of tablets or in solution.



Amphetamine

Action.—Applied locally amphetamine produces shrinking of the mucous membranes with a lessening of the nasal secretion. Excessive inhalation of the vapor will produce certain toxic symptoms such as stimulation of the central nervous system with wakefulness, an increase in blood-pressure and some cardiac weakness. Diuresis also occurs at times in susceptible persons.

Administered to man, benzedrine sulfate produces a stimulation of the central nervous system as shown by an increase in alertness and in motor and psychical activity, together with a decrease in fatigue, accompanied at times by insomnia. There is usually a rise in blood-pressure which may be prolonged and some slowing of the heart with irregularities such as extrasystoles or paroxysmal tachycardia. If atropine is given with amphetamine, the pulse rate is greatly increased. The drug has little effect upon the tone of the normal gastro-intestinal tract but will relax the organ if it is in a condition of hypertonicity. A moderate increase in basal metabolic rate occurs together with some loss of weight and an increase in the cellular content of the blood is explained by a possible vasoconstriction in the blood reservoirs in the body. Toxic doses produce hyperexcitability and insomnia followed by depression.

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There may be abdominal cramps and hematuria followed by collapse, convulsions and coma.

Injected into animals the drug produces a stimulation of the central nervous system with an increase in the rate and depth of the respiration. There is a marked increase in blood-pressure. With toxic doses there is a dilatation of the pupil, erection of the hair, salivation and tonic and clonic convulsions. On excised tissues the drug in high dilutions has little effect except some inhibition upon the intestinal musculature of the cat. In slightly more concentrated solutions it causes contraction of all smooth muscle.

Therapeutic Uses.—Benzedrine is used in a 1 per cent solution in liquid petrolatum for its vasoconstrictor effect in the upper respiratory passages. It is also used by inhalation combined with menthol and a flavoring oil. Used in this form it should not be employed at too frequent intervals as excessive use may cause restlessness and insomnia. Benzedrine sulfate (amphetamine sulfate) is often used in conjunction with homatropine as a cycloplegic. Internally it is employed in the form of tablets in doses of from 5 to 10 mg. for the treatment of narcolepsy, resulting usually in relief from the attacks of sleep and cataplexy. In some cases the doses named may have to be increased in order to produce the desired effects. In postencephalitic Parkinsonism used in conjunction with stramonium or scopolamine it has proved of value. It is also valuable in certain depressive psychopathic conditions, but such use should be confined to cases in institutions. It is useful in depressions characterized by apathy and psychomotor retardation and contraindicated in patients manifesting anxiety or hyperexcitability. It is not to be recommended as a remedy for sleepiness or fatigue, not only because of the danger of the formation of the habit, but also because it would remove a warning signal of overwork or overstrain in the individual. Then, too, the possible vasopressor effects would be undesirable and cases of collapse have been reported from such use. For the same reasons it should not be used as a central nervous stimulant to develop a sense of increased energy or increased capacity for work.

Amphetamine has been advocated in the treatment of obesity as a means of counteracting the depression induced by hunger, but its use for this purpose has not received official sanction.

The drug has been used in various spastic states of the gastro-intestinal tract and as an aid in the roentgenolographic study of this structure, but the evidence as to its value in these conditions is somewhat contradictory.

Amphetamine has also been used as an adjunct in the treatment of alcoholism.

The effective dose of amphetamine varies in different conditions. It is therefore desirable to begin with small initial doses (2.5 to 5 mg.) increasing gradually until the desired effects are obtained. The use of a small test dose to determine hypersensitivity to the drug is advisable.

The use of benzedrine sulfate is definitely contraindicated in conditions associated with hypertension, coronary artery disease and in states of excitement. The possibility of habituation to the drug must always be kept in mind.

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PREPARATIONS

B. P.

AMPHETAMINA, amphetamine, $C_6H_5 \cdot CH_2C \cdot H(CH_3) \cdot NH_2$, β-aminopropylbenzene.

AMPHETAMINÆ SULPHAS, amphetamine sulphate. Dose, 0.005 to 0.01 gram.

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4. Other Sympathomimetic Drugs

Various synthetic compounds which are more or less closely related chemically to epinephrine and ephedrine have been introduced into therapeutics as substitutes for the naturally occurring compounds. In general the changes which have been made in the molecule have rendered the compound more stable so that it is not so easily broken down in the body, thus prolonging its action and at the same time lessening its activity and toxicity. Numerous compounds of this series have been prepared and studied and it is possible to correlate their pharmacologic activity and chemical structure as first shown by Barger and Dale.

The molecules of epinephrine and ephedrine consist of a hydroxybenzene group with a side chain which is composed of an aliphatic amine. Only slight sympathomimetic activity is manifested by aliphatic amines, this activity being greatest in butyl amine. The introduction of a benzyl group enhances the sympathomimetic activity, phenylethylamine being the most active of the series. When a hydroxyl group is introduced into the benzene ring in the meta or para positions, the activity is still further increased. Still greater activity is manifested by compounds in which a methyl group is introduced into the primary amine group of the side chain and a further enhancement of activity is obtained by the introduction of a hydroxyl group attached to the carbon next to the benzene ring. Epinephrine and ephedrine are examples of com-

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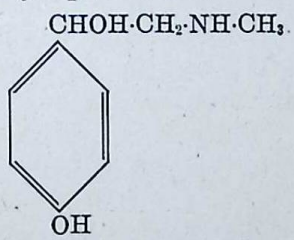
pounds the structure of which conforms to the requirements of maximal activity.

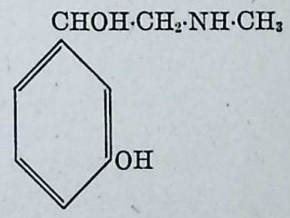
The excitatory and inhibitory effects which are manifested by epinephrine are not altered equally by changes in the epinephrine molecule. It is, therefore, possible to prepare compounds which exert primarily one or another of these actions, that is, which resemble more closely sympathin E and sympathin I in their activity. The goal of investigators has therefore been not only to produce more stable compounds with a prolonged action but also derivatives which, for example, might relax the bronchioles without exerting pressor and excitatory effects for use in asthma. Only a few of these compounds of therapeutic interest can be considered here. Indeed the actions of many of these compounds are such that they can not be designated as sympathomimetic in the strict sense of this term. However, because of their chemical relationship to the other sympathomimetic drugs they are usually thus designated and will be considered here.

Of the compounds discussed below only neosynephrine, kephrine and propadrine are included in New and Non-Official Remedies.

Synephrine and **neosynephrine** differ from epinephrine in that they have only one hydroxyl attached to the benzene ring instead of two as in epinephrine. They differ from each other in that in synephrine the hydroxyl is in the para position while in neosynephrine it is in the meta position. The former compound rotates polarized light to the right while neosynephrine rotates it to the left.



Synephrine



Neosynephrine

Synephrine (sympatol) as a vasoconstrictor is weaker than epinephrine but the constriction is more prolonged. In general it is from one-fiftieth to one one-hundredth as strong as epinephrine. Through an action upon the smooth muscle it causes relaxation of the intestine and of the bronchial muscle. It dilates the pupils and increases the tone of the uterus. Applied locally it constricts the smaller vessels, thus reducing congestion and swelling and in the nose it causes little irritation and sneezing.

Neosynephrine on account of certain advantages which it possesses over synephrin has replaced it in therapeutics. Injected into cats it causes an increase in blood-pressure which is considerably more prolonged than is that produced by epinephrine, and in man the pressure increase may be quite prolonged. Ergotamine, which will reverse the rise produced by epinephrine through paralysis of the motor receptive substances, has little effect in the case of neosynephrin, indicating that the constrictor effect is largely limited to the muscle in the vessel walls.

Applied locally to mucous membranes in a 0.25 to 0.5 per cent solution it constricts the smaller vessels and reduces congestion and swelling and

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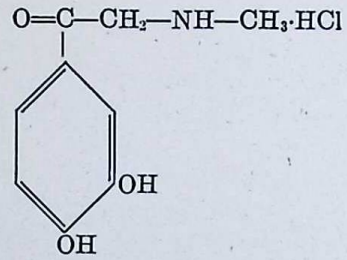
it may therefore be used in rhinitis and hay fever. It is also used to prolong the anesthesia produced by procaine and the other local anesthetics. Neosynephrine is also used to combat a drop in blood-pressure occurring during spinal anesthesia and in other acute hypotensive states due to vasomotor failure but it is useless in shock due to loss of circulating blood volume. It is also used as a mydriatic, 1 or 2 drops of a 1 per cent solution being dropped in the eye.

For hypodermic injection, neosynephrine is used in doses of 0.1 to 0.5 cc. of a 1 per cent solution. A $2\frac{1}{2}$ per cent ophthalmic solution, a 1 and 10 per cent emulsion and a $\frac{1}{8}$ per cent solution are also available for ophthalmic use.

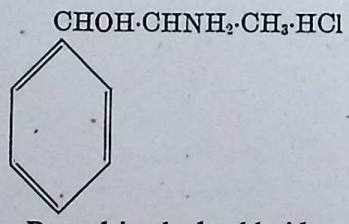


Kephrine hydrochloride

Kephrine hydrochloride, methylamino-acetocatechol hydrochloride, is the hydrochloride of a base resembling epinephrine. Kephrine differs from the latter only in the substitution of a keto (C=O) group for the secondary alcohol group (CH_2OH) of epinephrine.

In its **action**, kephrine hydrochloride is less powerful than epinephrine but its effects are more prolonged. It is used as a local hemostatic to arrest capillary bleeding. Its action comes on within two to three minutes and lasts for one to two hours. Since it is not absorbed in appreciable amounts, systemic effects, such as a rise in blood-pressure, do not follow its local application.

The drug is marketed in the form of a powder in suppositories or impregnated in gauze and bandages. The powder contains 5 per cent of kephrine hydrochloride in tricalcium phosphate; the suppositories consist of 3 parts of the drug, 1 part of extract of belladonna, and 96 parts of a suppository base; the bandages and gauze contain a gram of the drug per 3,000 square centimeters.



Propadrine hydrochloride

Propadrine hydrochloride, the hydrochloride of α-hydroxy, β-aminopropyl benzene, differs from ephedrine in that the methyl group attached to the NH of ephedrine is replaced by a hydrogen atom.

In **action** it resembles ephedrine closely. Like the latter it constricts the capillaries and shrinks the mucous membranes when applied locally.

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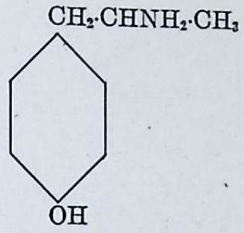
Its action is somewhat more prolonged than that of ephedrine and it is less apt to induce the anxiety effects observed following the use of the latter drug.

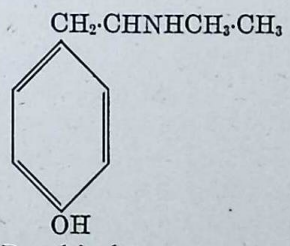
Propadrine hydrochloride is marketed in the form of an elixir, in capsules as a jelly and in the form of a 1 per cent aqueous solution. The solution is used as a spray or instillation, the jelly is applied locally and the capsules are administered orally in doses of 24 mg. every two to four hours. It is used in asthma and hay fever and to alleviate nasal congestion.



Paredrine

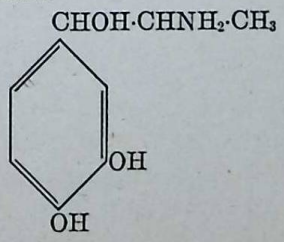
Paredrine, a proprietary preparation of methyl tyramine, is more stable than epinephrine and lacks the excitatory action of the latter on the central nervous system. It has a pressor action being about 1/50 to 1/100 as active as epinephrine in this respect, but is effective when administered orally as well as parenterally. It does not cause vasoconstriction when injected intradermally. The effects of paredrine on the vascular system resemble those observed pathologically in essential hypertension (Iglauer and Altschule).

Paredrine has been used clinically as a mydriatic in ophthalmology, as a pressor agent during spinal anesthesia and in Adams-Stokes syndrome.



Paredrinol

Paredrinol introduced under the trade-name "veritol" differs from paredrine in having a methyl group attached to the amino nitrogen. In action it resembles paredrine and like the latter also causes venous constriction with a rise in the peripheral resistance. It has about half the pressor activity of ephedrine.



Cobefrine

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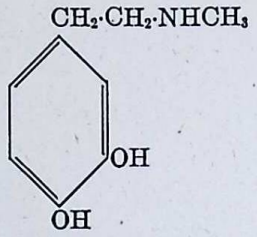
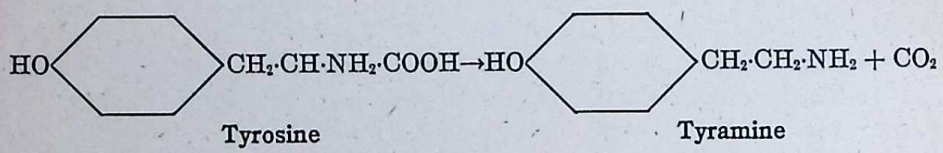
Cobefrine hydrochloride, a proprietary preparation of racemic, 3,4-dihydroxyphenyl propanolamine hydrochloride, is about half as effective as epinephrine in constricting the blood-vessels and raising the blood-pressure. It has been used locally in a 1 to 200 aqueous solution to control capillary hemorrhage and as a vasoconstrictor in local anesthesia.

Epinene hydrochloride, 3,4 dihydroxy-phenylethyl-methylamine hydrochloride, is only about a tenth as active as epinephrine but its action is more prolonged.



Epinene

Tyramine.—A number of other substances are known which resemble epinephrine in action and in chemical structure. Some are found in nature, being produced from the amino-acids by the removal of the carboxyl group; the amino-acids are formed in the decomposition of proteins and where this occurs in the presence of putrefactive organisms these bases are liable to occur. The best known of these is **Tyramine** or



hydroxy-phenylethylamine which is formed by decarboxylation of the amino-acid, tyrosine. These bases are all less active than epinephrine but otherwise present no significant divergence from it in their effects on the organism. Tyramine exerts less action on the terminations of the inhibitory nerves, and increases the blood-pressure more when it is injected hypodermically. Tyramine occurs in preparations of ergot and was first identified in putrefying flesh. It is not used therapeutically.

Methyl ephedrine, a tertiary amine, was first prepared by Negri and later isolated by Smith from Ephedra. On the blood-pressure, the effect of the methyl compound is about one-tenth as great as ephedrine and the heart is less accelerated. In dogs under luminal it will slow and deepen the respiration, but it does not antagonize the action of morphine upon the respiration. It does not stimulate the central nervous system as does ephedrine, and while it is less toxic for dogs and rabbits, the symptoms produced are much like those from ephedrine. Methyl ephedrine dilates constricted bronchi but the action is slightly weaker than with ephedrine.

Other members of this group of drugs which have been used in medicine are **arterenol,** which differs from epinephrine in lacking the

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methyl group attached to the amino-nitrogen, and **suprifen** which is the para hydroxy derivative of ephedrine.

Imidazole derivatives have also been prepared which exert actions similar in some respects to the compounds mentioned. Privine (naphthazoline) a proprietary preparation of α-naphthyl-2-methylimidazoline, for example, has been introduced for local application to relieve swelling of the nasal mucosa.

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F. ERGOT AND ITS ALKALOIDS

Ergot is a parasitic fungus (Claviceps purpurea) which grows on the rye (*Secale cereale*) and occasionally on other kinds of grain; more rarely on other plants. It is of some importance in therapeutics and also in toxicology, as the use of bread and meal containing it has frequently given rise to widespread epidemics.

Chemistry.—Ergot contains a remarkable group of interesting compounds some of which are only found in preparations of this fungus. The compounds of ergot include carbohydrates (mannite, trehalose, clavicepsin and manna), steroids (ergosterol), pigments (ergochrysin, ergoflavin), amino-acids (leucin, tyrosin, valin, histidin), putrefactive amine bases (putrescin, cadaverin, tyramine, histamine, choline, ergothionine, etc.), pyrimidine and purine bases (uracil, guanosine, nucleic acids, etc.) and the group of specific alkaloids now to be considered.

Crude preparations of ergot have been used for centuries by midwives as oxytocics. In 1875 Tanret first isolated a crystalline alkaloid which he called ergotinine. This constituent is inactive pharmacologically, being formed from its optical isomer, ergotoxin, which was first isolated by Barger and Carr in 1906. In 1920 Stoll isolated two more optical isomers, ergotamine and ergotaminine, the latter of which was inactive.

In spite of the isolation of these various alkaloids which were the product of many years of arduous research, the chemistry of ergot was still only partially solved, and it was still generally recognized that these alkaloids did not entirely replace the crude preparations. This was emphasized by the late onset of the effects on the uterus when the alkaloids were given as compared with the galenical preparations. When ergotoxine or ergotamine was administered, no contraction of the uterus appeared for almost an hour while with the crude preparations strong contractions would often be induced in from six to ten minutes. This

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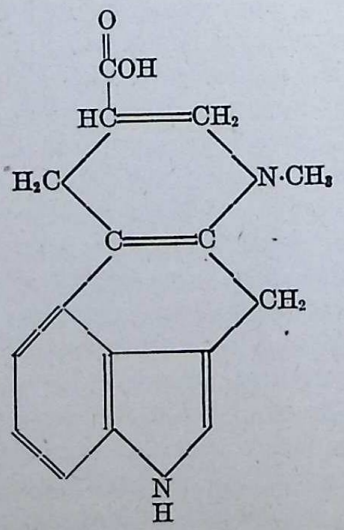
difference between the two groups of preparations was forcefully emphasized by Moir, who, employing a method which registered the contractions of the human uterus, was able to show that preparations made by watery extraction of the crude drug and therefore devoid of the commonly known alkaloids, were still active. In fact, powerful contractions of the uterus appeared within a few minutes after the drug had been given by mouth. It appeared, therefore, that there must be some active principle in ergot other than those which had been discovered and which was responsible for this early uterine response.

In 1935, Thompson, Stoll and Burckhardt, Dudley and Moir and Kharasch and Lagault isolated a third active principle which they designated as ergostetrine, ergometrine, ergobasine and ergotocine, respectively, but which is now known officially as ergonovine in the U. S. A. and as ergometrine in Britain. It too is convertible to an inactive optical isomer, ergometrinine. Two other pairs of alkaloids were subsequently isolated so that at present five pairs of alkaloids are known, one of which is levorotatory and pharmacologically active while the other member of the pair is dextrorotatory and relatively inactive. These isomeric pairs of alkaloids are the following:

Active	Inactive	Formula
Ergotoxine	Ergotinine	$C_{35}H_{39}O_5N_5$
Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
Ergonovine	Ergometrinine	$C_{19}H_{23}O_2N_3$

The members of each pair are interconvertible. The Ergotoxine and Ergocristine pairs are isomeric with each other as noted by their identical formulæ. Ergonovine and its isomer consist of a much smaller molecule than the other members of the series which is also reflected in the greater solubility of this pair in water, their relative insolubility in chloroform and their more basic character.



Lysergic acid

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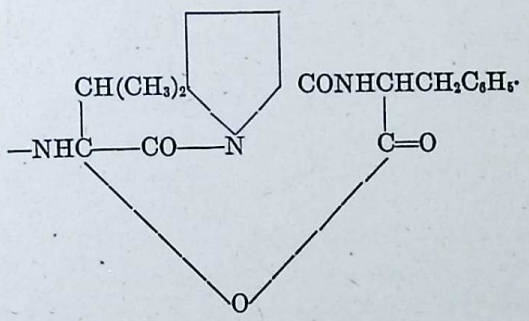
The members of each pair tend to crystallize together in equimolecular mixtures which for a time were mistaken for new compounds. Thus the combination of ergosine and ergosinine was designated as *ergoclavine;* ergotamine and ergotaminine were known as *sensibamine. Pseudo-ergotinine* is probably a mixture of ergotinine and ergotoxine.

All of the alkaloids listed above on hydrolysis give **lysergic acid** ($C_{16}H_{16}O_2N_2$) or its amide, ergine, so that this seems to be a common constituent although it is absent from Ergomonamine, $C_{19}H_{19}O_4N$, an alkaloid, not included in the above list, which has also been isolated from Ergot. It is assumed that isomerism in the lysergic part of the molecule accounts for differences in members of the same pair, while differences in the rest of the molecule account for the different pairs. Thus ergonovine consists of lysergic acid in which the OH group is replaced by $-NH-CH(CH_3)-CH_2OH$ while in ergotoxine the OH group is substituted by



Ergonovine and ergometrine are thus the hydroxyisopropylamide of lysergic acid and of isolysergic acid, respectively. Ergotoxine and ergotinine consist of lysergic and isolysergic acids, respectively in combination with proline, phenylalanine and hydroxyvaline. Ergotamine and ergotaminine contain hydroxyalanine in place of hydroxyvaline.

Toxicology.—Ergot has rarely given rise to serious **Acute Poisoning** in man, but in some cases in which it was taken to procure abortion the symptoms consisted in collapse, with a weak, rapid pulse, tingling, itching and coldness of the skin, unquenchable thirst, vomiting and diarrhea, confusion or unconsciousness, hemorrhage from the uterus, abortion and often icterus. Ecchymoses were found in the subcutaneous tissues and in many internal organs. Occasionally, after a single small dose, gangrene has supervened in small areas such as the toe-nails.

Given in therapeutic doses ergot has generally no effect except in pregnant women, in whom it often induces contraction of the uterus and evacuation of its contents. In some cases of fatal poisoning no abortion occurred.

Chronic Poisoning was formerly not uncommon, and in fact frequently gave rise to widespread epidemics, from the use of bread containing ergot after poor harvests and especially in wet seasons. Of late years

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these epidemics have become rare, but some of the "plagues" of medieval Europe may have been due to ergot poisoning.

The symptoms of ergotism are sharply divided into two groups: those of gangrene and those of nervous disorders. In some epidemics both the gangrenous and the convulsive forms are present, but, as a general rule, the epidemics in Western Europe were almost exclusively gangrenous in type, while in Eastern Europe the convulsive form almost invariably prevailed. The gangrene is generally developed in the limbs, especially in the fingers and toes; sometimes the whole arm or leg becomes cold and anesthetic, dark in color, and then dry, hard and shrunken, and falls off with little or no pain and no hemorrhage. Symptoms of such severity are rare, however, and in milder cases only the skin necroses. Gangrene of internal organs also occurs, resulting in cataract in the lens of the eye, or ulcers in the bowel and stomach, and sometimes affecting a whole organ such as a lung or the uterus. Abortion is seldom mentioned in the accounts of chronic ergot poisoning, and pregnancy seems in many cases to have run its ordinary course.

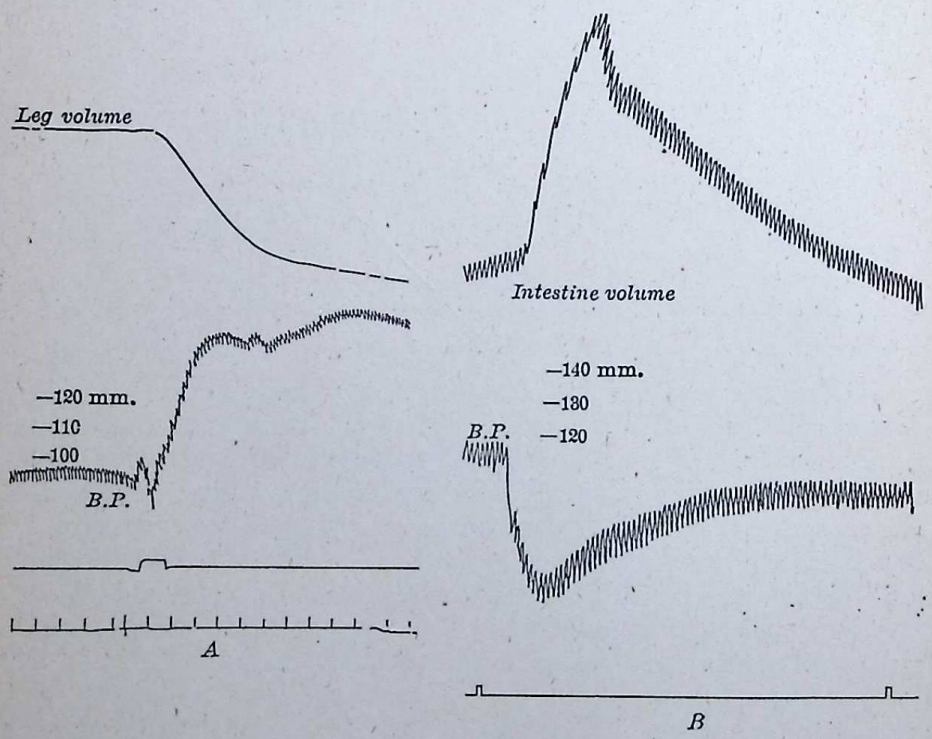

FIG. 44.—Figures illustrating the effects of ergotoxine on the blood-pressure (Dale). In *A* the injection induces a rise of blood-pressure (*B.P.*) with constriction of the vessels of the leg. In *B* a large dose of ergotoxine had been injected previously, and epinephrine injected at the point indicated now causes a fall of blood-pressure with dilatation of the intestinal vessels, illustrating the phenomenon known as vasomotor reversal.

In spasmodic ergotism the first symptoms are depression, weakness and drowsiness, often with headache and giddiness, painful cramps in the limbs and itching and formication of the skin. In severe cases paroxysmal convulsions set in, generally clonic, and often epileptiform,

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but leaving as sequelæ contractures in the limbs, or less often in the trunk muscles. Some intellectual weakness often follows recovery from ergot poisoning, this not infrequently amounting to complete dementia, but the disease was immediately fatal in a large proportion of cases in earlier times. The characters and distribution of these two forms of ergot poisoning have given rise to much discussion. The gangrenous form appears to be the more characteristic, and it has been suggested that the spasmodic form may have arisen in cases where ergot poisoning was complicated by starvation and possibly by epidemic nervous disease such as poliomyelitis or meningitis.

In mammals treated with ergot, restlessness, salivation, sometimes vomiting and purging have been observed. Depression and weakness, ataxia and clonic convulsions follow on larger doses, which prove fatal by paralyzing the respiratory center. Gangrene is common in the pig, in which the ears, the extremities, and patches of the skin of the trunk become dry and hard, and finally fall off. Extravasations of blood into the stomach and bowel and other organs have frequently followed the exhibition of ergot in mammals. In pregnant animals abortion is often induced, but not invariably, even when very large doses are given.

In fowls a characteristic train of symptoms is induced, and these animals have frequently been used as tests for the activity of ergot preparations. The cock becomes drowsy and dyspneic, and the comb and wattles become dusky purple in color. Vomiting or purging may follow and a curious ataxia is observed, the animal swaying to and fro and evidently maintaining its balance with difficulty. After large or repeated doses the comb becomes dry and hard and falls off, and a similar gangreme may attack the legs, tongue, or wings. The animal refuses food and becomes weak and somnolent, but may recover if the treatment be stopped. The gangrene of ergot poisoning arises from the prolonged constriction of the vessels by the ergotoxine and ergotamine. Chronic ergot poisoning in the rat gives rise to neurofibromas on the ears.

Action.—Ergotoxine, ergotamine, ergosine and ergocristine resemble one another closely in their pharmacological action and hence may be considered together. Ergonovine differs from these and will receive special attention. The study of the action of ergotamine and ergotoxine in the living organism has shown that these alkaloids resemble epinephrine in some of their effects, and like it act on the myoneural junctions of the true sympathetic nerves. But while epinephrine stimulates these junctions indiscriminately whether they are motor or inhibitory in character, the ergot alkaloids act on the inhibitory junctions only to a slight degree but stimulate the motor myoneural junctions in small doses and paralyze them in large amounts. They are less powerful than epinephrine, but the effects last longer and can be elicited by hypodermic injection or by administration by the mouth. The physiological action of ergotoxine and of ergotamine is much the same both qualitatively and quantitatively, the main point of difference being in the action on the medullary centers. Ergotoxine shows slightly greater activity than

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ergotamine in inhibiting the action of epinephrine and hence it is used in pharmacological studies where it is desired to dissociate the excitatory from the inhibitory action of epinephrine. Ergosine appears to be even more potent than ergotoxine in this respect but is less readily available. Ergotamine is only about two-thirds as toxic to mice as ergotoxine.

Circulation.—Ergotoxine and ergotamine injected intravenously cause an abrupt rise in blood-pressure which is obviously due to action on the peripheral vessels, for it occurs after section of the splanchnic nerves, and is accompanied by constriction of the vessels of the abdominal cavity and the limbs, as may be shown by oncometer and plethysmographic records (Fig. 44, *A*). The heart is often accelerated at first and then slowed, partly from the vagus center being stimulated by the high blood-pressure and partly by a direct action on the heart muscle. Sometimes the slowing of the heart may be so marked as to lower the blood-pressure and thus to conceal the effects of the vasoconstriction on the tracing.

The rise in pressure is to be ascribed to stimulation of the constrictor nerve terminations in the vessel walls and is strictly analogous to that observed under epinephrine. The extent to which it is developed varies in different animals, being well marked in the cat, dog and fowl and observed only with difficulty in the rabbit and monkey.

Ergot preparations injected intravenously sometimes fail to increase the blood-pressure if they contain little of the specific alkaloids and large proportions of histamine, which dilates the capillaries (page 522). As a general rule an intravenous injection of a crude ergot preparation, as distinguished from the alkaloids, is followed by some fall in pressure, and then by a slower rise above the normal.

The ergot alkaloids have little effect in constricting the vessels when applied locally, therefore, absorption is not so much retarded as by epinephrine and ergot action may thus be elicited by oral administration.

The heart is not acted upon so strongly as the vessels by ergotoxine but the contractions are strengthened while the rhythm is slower in some degree; it is uncertain how far this arises from direct action of the cardiac muscle and how far the accelerator terminations are involved. Crude ergot preparations generally slow and strengthen the heart when injected intravenously; sometimes a muscarine action is induced by the presence of acetylcholine. The terminations of the inhibitory nerves of the heart are not paralyzed or weakened in any way by ergot and indeed according to Rothlin the activity of the vagus is augmented by ergotamine while in the case of the depressor nerve the reverse is true.

Ergotamine causes a moderate increase in the pressure of the cerebrospinal fluid following the intravenous injection of small doses. An increased flow of blood through the brain is also found, this increase being in all probability secondary to the increase in general systemic blood-pressure.

Stomach and Intestine.—Ergotoxine and ergotamine in small doses have little effect on the movements of these organs, since the sympathetic nerves are inhibitory and therefore escape its influence; under

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ergot, vomiting and diarrhea often occur in animals; in man the action on the digestive organs is seldom noticeable.

The **Pupil** undergoes a powerful constriction when ergot is injected intravenously, sometimes after a momentary dilatation. This constriction is not affected by atropine and arises from the direct action of ergotoxine on the muscle fiber; in the rabbit, however, the pupil is dilated, perhaps owing to the excitement and increased movement.

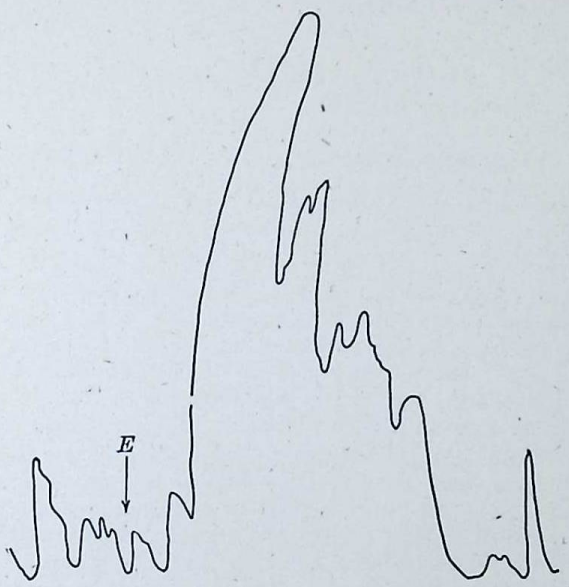

FIG. 45.—Tracing of the movements of the uterus under ergot injected intravenously at the point *E*. Contraction is indicated by an upward movement of the lever.

The **Respiration** is often greatly accelerated in poisoning in animals apparently from stimulation of the center, though this may be aided by the increased movement and high temperature.

The **Temperature** rises greatly in the cat and rabbit under ergotoxine while in the rat and mouse it often falls. In general, small doses cause a fall while larger doses induce a rise in temperature. This effect is probably a result of the action of the drug on the temperature regulating center. It is absent after removal of the brain, presumably owing to the destruction of the heat-regulating center. Ergotamine is only half as effective as ergotoxine in its capacity to alter the body temperature.

In some animals the hair rises owing to the stimulation of the sympathetic terminations in the pilomotor muscles.

The most important effect of ergot, however, is exerted on the **Uterus**, in which it causes a powerful contraction which lasts for a short time and is followed by a slow relaxation interrupted by numerous new contractions, a lasting effect on the irritability being induced (Fig. 45). The innervation of the uterus, both motor and inhibitory, is derived from the sympathetic; but ergotoxine, stimulating only the motor fibers, always causes contraction, the inhibitory ones remaining unaffected by it.

The uterus thus reacts to ergot in a way precisely analogous to the arterioles, and it is noteworthy that from therapeutic doses it is from

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the uterus alone that any obvious symptoms are elicited. The alimentary tract is but little affected, and the rise of blood-pressure is not easily observable in the circumstances in which ergot is usually exhibited. The contraction of the uterus in pregnant animals causes the descent of the fetus toward the os, and in suitable doses ergot induces abortion. If the dose injected is small, the rhythmic contractions are accelerated and strengthened, or if the uterus is at rest, ergot may arouse it to rhythmic contraction. As the dose is increased, the contractions become more powerful and last a longer time, until with a large injection the uterus may contract very powerfully and remain in this position for many minutes.

The secondary paralyzing action of ergotoxine and ergotamine on the myoneural junctions is elicited only by large doses and does not occur in the therapeutic use of ergot; large quantities of ergot often elicit this effect in experiments, however. This paralysis was originally believed to affect only the motor sympathetic neurons, while the inhibitory ones were, according to this view, left unaffected and stimulation of a mixed motor and inhibitory nerve, or the injection of epinephrine, caused inhibition only. This view of action of the ergot alkaloids being confined to the motor sympathetics is undoubtedly true when applied to the use of moderate doses of the drugs but with the employment of large doses a further action upon the inhibiting nerves is also seen as described below. Thus, after a moderate dose of these alkaloids, epinephrine may lower the blood-pressure (Fig. 44, *B*), where previously it increased it by stimulating the constrictor nerve ends; these are now unable to react due to the paralyzing action of the ergot alkaloids, but the dilator nerve ends are more resistant, and epinephrine stimulating them dilates the vessels. Epinephrine also acted on the dilators before the ergotoxine injection, but the effect of this stimulation was masked by the simultaneous stimulation of the more powerful constrictors. The same reversal of effect by ergotoxine is seen if the splanchnic nerves be stimulated. The motor splanchnic fibers to the intestinal sphincters and bladder and other similar motor sympathetic fibers are similarly paralyzed by ergotoxine in fairly large doses, and stimulation of the nerves or the injection of epinephrine has now no effect on them. The fibers from the cranial and sacral nerves, however, are uninjured. Similarly, stimulation of the cervical sympathetic no longer dilates the pupil or elicits salivation in ergotoxine poisoning because the connection with the muscle and gland is broken, but the motor oculi and chorda tympani, being cranial nerves, remain normal. Both motor and inhibitory nerves of the uterus are sympathetic, and ergotoxine in certain amounts paralyzes the motor while leaving the inhibitory intact, and stimulation of the hypogastric nerve or epinephrine now causes inhibition and relaxation. The accelerator nerves to the heart are sympathetic, but it is difficult or impossible to throw them out of action completely with ergotoxine.

In contradistinction to the view of the action of the ergot alkaloids being exclusively confined to the motor sympathetic endings as described above, Rothlin showed that ergotamine not only paralyzes the motor sympathetic fibers but also acts on the inhibitory terminations as well. It thus prevents not only the motor but also the inhibitory effects which follow the injection of epinephrine. This was shown by allowing solutions of ergotamine to act upon certain excised tissues which were normally inhibited by epinephrine. Following the use of such solutions the action of epinephrine was entirely absent. In the case of the intestine of the guinea-pig and of the rabbit a concentration of ergotamine twice that of the epinephrine was needed in order to offset the action of the latter drug. In the intact animal the same reaction was also shown. For instance in the case of the intestine of the dog and the rabbit, minimum amounts of ergotamine are sufficient to prevent the normal inhibitory epinephrine effects. The ease with which the endings are affected by ergotamine differs considerably in different animals, the guinea pig and the rat being especially resistant. Accord-

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ing to Rothlin, therefore, ergotamine and epinephrine occupy the same relationship in respect to the sympathetic nerves that atropine and pilocarpine do for the parasympathetics.

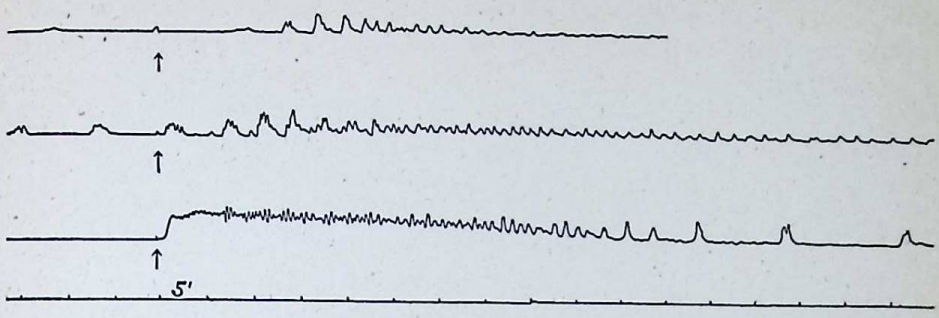

FIG. 46.—The effect of ergonovine upon the human uterus. Tracings obtained from 3 patients each on the seventh postpartum day. In each case a rubber balloon was placed within the uterine cavity and connected with a bellows recorder. To each patient 0.2 mg. of ergonovine tartrate was administered. To patient yielding the top curve it was given by mouth; to patient giving the middle curve, by subcutaneous injection, and the lowest curve, by intravenous injection. The time intervals are five minutes. In the last 2 cases the effects lasted more than two hours, while in certain other patients the increased contractions were plainly observable for a much longer time. (Gardner and Bradbury.)

In this connection mention may be made of **Fourneau 933** (2-piperidinomethyl-1, 4-benzodioxan) which in contrast to the sympathicolytic action manifested by ergotoxine and ergotamine is **adrenolytic** in action. That is, it blocks the response of the effector organs to epinephrine but not to adrenergic nerve impulses. After the injection of the ergot alkaloids, the effector cells respond neither to adrenergic nerve impulses nor to epinephrine and hence these drugs are designated as **sympathicolytic.**

Some **Tolerance** is acquired for ergotoxine when it is injected repeatedly into animals.

Ergonovine resembles the other members of the group in certain of its actions. It shows a definite sympathomimetic effect with little or no inhibition of epinephrine action. In general it is only approximately one-fourth as toxic as ergotamine for mice and rabbits and one-tenth as toxic for cocks, but nearly equally toxic for cats. The toxic symptoms resulting from its use resemble closely those produced by the older alkaloids and are apparently due to the lysergic component of the molecule judging from the toxicity of ergine, the amide of lysergic acid. The symptoms from ergonovine are mainly those due to central nervous stimulation, weakness, tremors, excitement, convulsions, together with signs of sympathetic stimulation such as mydriasis, exophthalmos, erection of the hair and tachycardia. The symptoms resulting from sympathetic stimulation seem to be due almost exclusively to central action. Its most important action is upon the uterus where its effects are prompt and vigorous whether it is administered by mouth or intravenously. The outstanding features of the action of ergonovine on uteri are shown in the puerperal period where its prompt action and effectiveness in small doses distinguish it from the other alkaloids. This action on the uterus is not only seen in animals, but also occurs in the

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human subject, where after oral or subcutaneous administration strong contractions of the uterus appear within a few minutes.

The uterine action of ergonovine is the only appreciable effect which follows the use of moderate doses; the unpleasant side actions being only rarely encountered clinically. The promptness of its action and effectiveness when administered orally has made it a highly desirable ecbolic for clinical use. It increases the tone, rate and amplitude of rhythmic uterine contractions.

On the isolated quiescent strips of human uteri and fallopian tubes ergonovine has little effect, but it induces vigorous contractions in similar strips of the postpartum uteri of guinea pigs.

Ergonovine raises the blood-pressure in rabbits and spinal cats but usually lowers it in anesthetized cats and dogs. It has little effect upon the heart. It quickens the respiration but lessens the respiratory volume. The temperature is lowered in rats and mice, but it causes hypothermia in rabbits whereas in these animals ergotamine in small doses leads to hypothermia and in large doses to hyperthermia. Ergonovine exhibits some signs of a peripheral action upon the sympathetic system, such as mydriasis, relaxation of the isolated intestine of the rabbit and some increase in the blood sugar of rabbits and dogs, but the symptoms seen in the intact animal ascribable to a sympathetic action are mainly central in origin.

The principal difference in action between the ergonovine and the other alkaloids is that it exerts no paralyzing effect upon the sympathetic nerves so that while the sympathetics are stimulated, causing the increase in blood-pressure, they are not paralyzed so that the vasomotor reversal phenomenon is not seen. Nor are the other effects of sympathetic nerve stimulation inhibited by it as they are by the other alkaloids. A striking point of difference between ergonovine and the other alkaloids is that while the former will produce cyanosis of the cock's comb, it shows less tendency to produce gangrene than ergotoxine or ergotamine. It will be seen, therefore, that the greatest clinical value of ergonovine is in the field of obstetrics and that it is without value in those conditions in which an action upon the sympathetic nerves might be required. Ergonovine may, however, induce a slight rise in blood-pressure when used in therapeutic doses.

Assay.—Ergot and its preparations may be assayed by a variety of methods. The indole group of the lysergic acid component of the molecule forms a blue color with para-dimethylaminobenzaldehyde but this method fails to distinguish ergonovine from the other members of the group. The Broom-Clark method is based on the inhibition of the action of epinephrine on the isolated rabbit's uterus, but ergonovine does not induce this action. The official pharmacopeial method utilizes the cock's comb which measures the total active alkaloids.

Therapeutic Uses.—Ergot is used very extensively in obstetrics to promote the contraction of the uterus, but considerable divergence is met with in the views of different authorities as to the special indications for its exhibition.

The principal use of ergot is to prevent postpartum hemorrhage for

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which purpose a full dose is given as soon as the second stage of labor terminates. However, it should not be given until the placenta has been delivered since its use during labor may cause rupture of the uterus or asphyxia of the child. Ergot is also used to prevent "after-pains" and to inhibit bleeding in menorrhagia and metrorrhagia. It is administered orally in the form of the fluid extract in doses of 2 cc. A liquid extract (ergot aseptic) intended for injection is also available. It is administered in doses of 1 to 2 cc. intramuscularly.

When ergot or its alkaloids are used, care must be taken that these drugs are not given for more than a brief period as several cases of gangrene of the extremities have been reported due to neglect of this precaution.

Ergot hinders postpartum hemorrhage, chiefly by promoting the contraction of the uterus. In other forms of hemorrhage—from the stomach, intestines, kidneys, lung or uterus—in which the bleeding point cannot be reached, it is often advocated in the belief that it contracts the walls of the vessels and thus arrests the flow of blood, but it may be questioned whether ergot exerts any influence whatsoever in these cases. The essential treatment is rest with or without morphine or opium.

The effect of ergot in inducing contraction of the uterus has been used in the treatment of subinvolution and the process certainly seems to be favored by it. The prolonged treatment of this, or of any other condition, with ergot is to be deprecated, for if the drug is active at all, it may induce gangrene. This is especially true when the alkaloids are employed.

Ergotamine tartrate (Gynergen) is widely used as a treatment for **migraine** and severe headaches of a periodic type. Its administration has been followed by relief in a large proportion of cases, although in a certain number no improvement follows. Relief usually follows ten minutes or more after its subcutaneous administration.

The pain of migraine attacks is believed to be produced by distention of the cranial arteries and the termination of these attacks by ergotamine is therefore attributed to its action in constricting these arteries and thus reducing the amplitude of the pulsations (Graham and Wolff). Factors which decrease the pulsation amplitude decrease the headache and *vice versa*. Ergotamine reduces the pulsation by about 50 per cent, at the same time reducing the headache, and observations and photographs made before and during the action of ergotamine show vasoconstriction of the temporal and meningeal arteries.

In migraine, ergotamine tartrate is injected in doses of 0.25 mg. subcutaneously, followed in two or three hours by a full dose of 0.5 mg. if no untoward effects have occurred and if the first injection has not been effective. Two or three tablets (each containing 1 mg.) may be given orally to be repeated hourly for two or three hours but this method of administration is less effective than the parenteral route.

Caution should be exercised in the use of ergotamine. Cases of gangrene have followed its continued use over a period of some days and death in cases of overdosage. Preëxisting sepsis or obliterative vascular

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disease, especially of the coronary vessels, is a contraindication to the use of the alkaloid. It should also be used with caution in the presence of arteriosclerosis. Even small doses may induce distressing and serious effects in susceptible individuals.

Ergotamine tartrate is also used in place of ergot for inducing uterine contractions and to stop uterine hemorrhage. For this purpose it is administered in doses of 0.25 mg. intramuscularly or 1 mg. orally two to four times daily.

Ergonovine in the form of its maleate (Ergotrate) and hydracrylate (Ergotrate H) is now used widely for its oxytocic effects in place of posterior pituitary liquid and other ergot preparations. It may be given intravenously in a dose of 0.2 mg., for immediate effects but is also promptly effective when given by intramuscular injection or orally. Its lower toxicity, rapid onset of action and sustained action have recommended it over other ecbolics. In delayed involution of the uterus during the puerperium the oral administration of 0.2 to 0.4 mg. three times daily has been recommended.

Preparations

U. S. P.

Ergota, the dried sclerotium of *Claviceps purpurea*, the potency of which is such that 1 gram is equivalent to not less than 0.5 mg. of the U. S. P. Ergotoxine Ethanesulfonate Reference Standard. The cock's comb method is used for the bio-assay.

Fluidextractum Ergotæ. Dose, 2 cc.

Ergonovinæ Maleas, $C_{19}H_{23}N_3O_2.C_2H_4O_4$, the maleate of ergonovine, an alkaloid obtained from ergot. Dose, 0.5 mg.

Tabellæ Ergonovinæ Maleatis, tablets of ergonovine maleate. Dose, 0.5 mg.

Injectio Ergonovinæ Maleatis, a sterile solution of ergonovine maleate for injection. Dose, 0.2 mg. intramuscularly or intravenously.

Ergotaminæ Tartras $(C_{33}H_{35}N_5O_5)_2.H_2C_4H_4O_6$, the tartrate of ergotamine, an alkaloid obtained from ergot. Dose, 0.5 mg.

Tabellæ Ergotaminæ Tartratis, tablets of ergotamine tartrate. Dose, 0.5 mg.

B. P.

Ergota.

Ergota Præparata, Prepared ergot. Dose, 0.15 to 0.5 gram.

Extractum Ergotæ Liquidum, Liquid extract of ergot. Dose, 0.6 to 1.2 mil.

Ergometrina, ergometrine, $C_{19}H_{23}O_2N_3$. Dose, 0.0005 to 0.001 gram; by intramuscular injection, 0.00025 to 0.0005 gram; by intravenous injection, 0.000125 to 0.00025 gram.

Ergotoxinæ Æthanosulphonas, Ergotoxine Ethanesulphonate, the ethanesulphonate of ergotoxine. Dose, 0.0005 to 0.001 gram.

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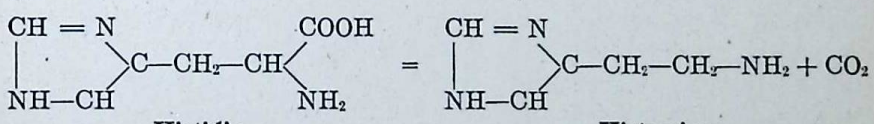
G. THE HISTAMINE GROUP AND ANAPHYLAXIS

Histamine is an amine derived from the amino-acid histidin by the removal of the carboxyl group, and structurally is β-iminazolyl-ethylamine.



Histidin Histamine

Histamine may be found wherever protein is broken down into its component amino-acids in the presence of putrefactive organisms; thus it occurs in some quantity in the intestinal contents and in the putrefaction of meats and has been isolated from preparations of ergot. It occurs in all the tissues but is present in highest concentration in the lungs. The leukocytes also contain an appreciable amount of histamine.

Allergy and Anaphylaxis.—The wide distribution of histamine in the body and the fact that the symptoms of secondary shock from severe injury resemble those induced in animals by histamine so closely, suggested that they are due to the liberation of histamine or similar poisons in the injured tissues. Another form of poisoning which resembles that of histamine very closely was first described by Richet and called by him **Anaphylaxis.** If an animal receives an injection of any harmless foreign protein, it presents no symptoms whatever; but if the same protein is injected again after an interval of about ten to fifteen days, a severe or fatal reaction may result. This anaphylactic reaction is very specific for each protein; for example, if the first, or sensitizing injection consists of horse serum, then the second injection must contain horse serum, that of any other animal causing little or no reaction. The sensitiveness to a second injection remains for many months, in man

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perhaps throughout life, and this has become of great importance of late years, since an injection of one of the antitoxic sera in childhood may suffice to induce reactions in adult life if a second treatment is necessary with serum from the same species of animal. When an animal recovers from even slight anaphylactic shock, no reaction occurs from a further injection; the animal is said to be desensitized.

Many unusual reactions presented by individuals to certain foods or to exposure to dusts and pollens which are harmless to most people, are now believed to be due to their having been previously exposed to these and having become sensitized to them. Anaphylaxis is induced only by proteins or by compounds which react with proteins to form a protein complex.

Several explanations of anaphylactic shock have been given; according to one of these, the first or sensitizing injection leads to the development of a ferment-like substance which modifies the protein injected (antigen); on the second injection this ferment decomposes it rapidly into a poisonous "anaphylotoxin" which produces the symptoms, just as such a drug as histamine does. On the other hand, Dale holds that the sensitizing injection leads to the formation of a new antagonistic body, precipitin, which penetrates into the cells of unstriated muscle and other tissues; when the second injection is made, the antigen penetrating into the cells reacts with the precipitin, causing cellular injury and freeing histamine and other substances, the action of these other substances being responsible for those symptoms which occur in anaphylactic shock and are not produced by histamine. This view is in harmony with many other facts known about the behavior of antigens and has been supported by experiments in which the involuntary muscle reacted to the second injection after all trace of protein had been washed out of the vessels, and in which any anaphylotoxin in the blood must have been removed also. In anaphylaxis the cells are peculiarly sensitive to the presence of the antigen; it is true that this sensitiveness arises from the formation of a precipitin in the blood and tissues as a result of the first injection, but this is not toxic in itself, but only reacts with the antigen. This precipitin may be transferred by transfusion to a second animal, which then becomes sensitive to the antigen, though it has never come in contact with it directly. After the shock has been recovered from, no second attack is caused by a second injection of antigen, since all the precipitin has been combined already.

The similarity of the symptoms induced by all of these has suggested that they arise from a single substance, and histamine has been looked for repeatedly in anaphylaxis. In anaphylactic shock in guinea-pigs and dogs there is a very considerable increase in histamine in the blood. In the dog the amount is even eighty times the normal value, the peak of the concentration being in the first ten minutes. The fall in blood-pressure under these conditions is greatest during this time and it remains low until the disappearance of the excess histamine from the blood. In anaphylactic shock in the calf and in the horse the histamine content of the blood is reduced in contrast to the finding in guinea pigs and dogs. These contradictory findings do not necessarily indicate

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that in certain species histamine is not released in anaphylactic shock as we know little about its fate in the blood under those conditions, so all that can be said is that in the horse and the calf it does not accumulate in the blood in anaphylaxis.

Histamine antigens have been prepared by coupling histamine to various proteins. The injection of these compounds into animals induces hyperimmunization and the production of antibodies which are partially specific for the histamine hapten. The immunized animals display a marked degree of resistance to anaphylaxis.

Compounds have recently also been prepared which protect guinea pigs against fatal doses of histamine, which decrease the cutaneous vasodilating action of histamine, and which inhibit the secretion of acid by the stomach following the injection of histamine. Beta dimethylaminoethyl benzhydryl ether hydrochloride **(benadryl)** and N^1-pyryl-N^1-benzyl-N-dimethylethylene diamine hydrochloride **(pyribenzamine)** are two of these anti-histamine compounds which have been introduced recently into medical practice. They are administered orally in 50 mgm. tablets. The value of these compounds in the treatment of allergic disorders must await further study.

Symptoms of histamine poisoning have arisen in man from attempts to substitute it for ergot in obstetrics. At the point of injection it causes swelling and infiltration of the tissues which itches or is painful on pressure. Headache and depression are complained of, the face and head are congested, the conjunctiva is blood-shot and painful. The breathing is dyspneic, and sticky mucus is expectorated. The blood-pressure falls while the pulse is accelerated. Nausea is developed and the stomach is found to be strongly contracted when examined by x-rays. Finally the impairment of the circulation progresses to profound collapse and shock, especially on any exertion being attempted. The decrease in blood-pressure may be profound; 4 mg. lowering it in one case from 197/100 mm. Hg to 80/45 mm. Hg. Larger doses caused marked cardiac arrhythmia.

In animals the effects of histamine vary with the species. In the guinea pig an intravenous injection may be fatal within a few minutes owing to spasm of the bronchial muscle which prevents expiration, so that the lungs are found fully distended and do not collapse when the thorax is opened. In the rabbit the most severe symptoms arise from the constriction of the pulmonary arterioles, which causes dilation of the right ventricle and finally arrests the circulation. In the cat and dog histamine induces vomiting and purging, profuse salivation, dyspnea and collapse; the pupils are constricted and the uterus contracts powerfully.

In all of these animals the **Central Nervous System** appears to be somewhat depressed, though this may be overshadowed by the symptoms arising from the peripheral organs.

The action on the **Circulation** is complicated and differs in different animals. The arterioles are contracted and the blood-pressure is therefore increased in the herbivora, while in the carnivora this preliminary increase is absent or transient and is soon followed by a large fall in

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pressure from dilation of the capillaries. The rise in pressure is due to direct action on the muscle; which is not prevented by ergotoxine, the subsequent fall, to a loss of tone in the capillary walls, which become distended with blood; the animal is bled into its own capillaries and this leads to the symptoms of collapse from insufficient blood returning to the heart and the arterial side of the circulation. The pulmonary vessels remain constricted however, and this is another factor in disturbing the circulation. In the cat, the capillary action is diffused fairly evenly throughout the systemic circulation; in the dog, it is more marked in the liver than elsewhere, as is shown by the swollen and tense condition of that organ.

In man, the slow intravenous infusion of histamine at the rate of 0.02 to 0.04 mg. per minute induces no change in the systolic blood-pressure, an increase in cardiac output compensating for the vasodilation.

In the herbivora, the action on the capillaries is absent, so that histamine increases the blood-pressure through constriction of the arterioles; later it becomes irregular through the asphyxia.

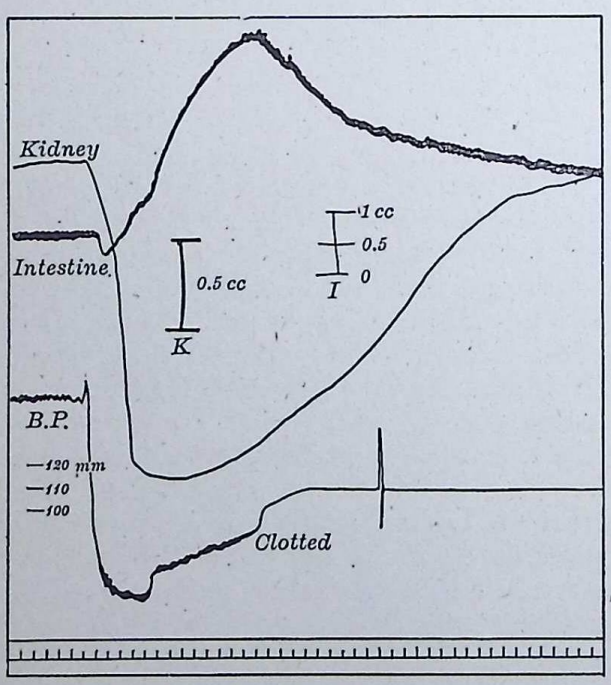

FIG. 47.—The action of histamine on the blood-pressure (*B.P.*) and on the volume of the intestine and kidney in the cat. The injection causes a marked fall in the blood-pressure which is due to dilatation of the intestinal capillaries. The kidney vessels are constricted. (Dale.)

The capillary action is not developed when histamine is added to the fluid perfused through surviving organs of the cat in the ordinary way, apparently because some receptor in the capillaries has become unresponsive through the failure of the oxygen and epinephrine supply; in these experiments, histamine lessens the flow through the vessels by constrict-

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ing the arterioles. When special measures are taken, however, the dilation of the capillaries can be shown in these experiments also (Dale and Richards). The shock symptoms in carnivora are increased by anesthetics, and this is true also of secondary shock from injury. The heart is increased in strength though it may be slowed in rate from a direct action on the heart muscle, but as the fall of pressure is developed, the beat may become slower from an insufficient supply of blood.

In the excised perfused hearts of both rabbits and cats histamine causes both augmentation and acceleration, diminishing the coronary outflow in the rabbit, but increasing it in cats. This latter action may be due to dilatation of the capillaries (Gunn).

The **Respiration** does not seem to be affected through the center; the asphyxia in the herbivora is induced by constriction of the bronchi from histamine acting on the bronchial muscle directly; this action is hardly affected by atropine, showing that it is not dependent on the nervous mechanism; on the other hand, it is antagonized to some extent by epinephrine, which inhibits the bronchial muscle, and by anesthetics, especially urethane, which has a special weakening action on the bronchi.

The **Stomach, Intestine and Uterus** contract more powerfully or may pass into spasm, and as this effect is not counteracted by atropine, it probably arises from direct action on the muscle; the uterus especially is exceedingly sensitive to the presence of histamine.

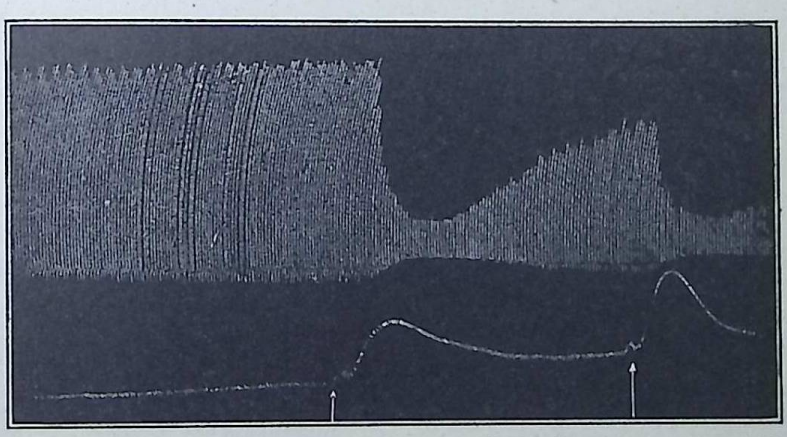

FIG. 48.—Action of histamine on the bronchi and blood-pressure of a rabbit. The expansion of the lungs on inflation is greatly reduced (upper tracing) from the contraction of the bronchi. The blood-pressure rises with each injection. At the arrows, intravenous injection of histamine. (Gunn.)

The **pupil** is contracted, apparently from central action, for this does not occur under anesthesia.

The accumulation of the blood in the capillaries and increased permeability of the capillary walls facilitate the escape of the plasma of the blood, so that the red cells are increased in proportion. There is an increase in certain of the chemical constituents of the blood, such as the calcium, phosphate, non-protein nitrogen, and sugar; but the increased concentration of the blood will probably account for some of these changes.

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Many **Glands** secrete under histamine—the salivary, gastric, pancreatic and lacrimal; this action is prevented or greatly diminished in the salivary glands, and presumably in the others, by atropine, but not by section of the parasympathetics, so that the secretion is probably caused by stimulation of the ganglia or the terminations of the postganglionic fibers. In the case of the gastric secretion, the increase is mainly one of water, hydrochloric acid, and other inorganic constituents without affecting the secretion of the enzymes.

Histamine has been isolated from acid extracts of the pyloric mucosa and is the secretory excitant present in such extracts. A histamine-like substance has also been found in the gastric juice of normal persons but the amount present is small.

Histamine apparently is destroyed in certain tissues by an inactivating substance which has been designated **histaminase.** This enzyme has been found in many tissues and organs, the largest amount being in the intestines and kidneys while none was found in the stomach, heart or skin. Attempts have been made to use preparations containing histaminase in the treatment of allergic conditions. However, inasmuch as this enzyme is destroyed in the gut it is difficult to see how it could possibly help to reduce the histamine content in the tissues where the latter exerts its undesirable effects.

Histamine which is liberated in the body by cell destruction or by nerve stimulation, or which is injected intravenously, is taken up by the tissues and then slowly passed into the blood. The heart-lung preparation of a dog can inactivate large amounts of histamine. The major part of blood histamine in the dog has been shown to be held in combination in the white blood cells. In the rat, injected histamine disappears rapidly from the blood. In the various tissues, aside from the kidney, histamine disappears rapidly during the first half hour after its injection. In the kidney during this time the amount remains almost unchanged, but in the second half hour and subsequently the amount drops very rapidly.

The **local action** of histamine is seen when it is applied to a scratch on the skin or by subcutaneous injection, and consists in dilation of the capillaries, leading to redness, swelling, and the exudation of plasma into the skin; this is apparently due to local capillary dilation and suggests that the wheal caused by local injury may arise from the liberation of bodies with similar action.

Lewis has described the local skin reaction as a "triple response;" a vasodilatation, a diffuse flare with a diameter of about 3 cm., and an area of local edema. The maximum response is attained in about five minutes and the effects have passed off in about an hour. When the nerves of the skin have degenerated the flare does not appear but the edema is present. These phenomena have been ascribed by Lewis as being due to the H-substance; the action of which is not unlikely to be due, at least in part, to histamine.

The characteristic action of histamine is the powerful contraction of the unstriated muscle, which is developed in the **uterus**, and in the **bronchi** in some animals. A remarkable exception to this contractor

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action has been observed in the rat's uterus, which is inhibited by histamine. The muscle of the alimentary tract and arterioles responds less strongly and the iris and bladder are not affected directly. In the carnivora there is extreme dilation of the capillaries, except those of the lungs, apparently from direct action on the walls. The peripheral nervous mechanism of the glands is stimulated to some extent, and there is some narcotic action on the brain.

Therapeutic Uses.—Histamine is employed in clinical medicine as a gastric secretory stimulant, especially as a diagnostic agent to distinguish between true and false achylia. The change in secretory activity which it produces is, as pointed out earlier, entirely confined to an increase in the acid component of the gastric juice. Histamine is a very efficient agent to employ in such tests but care must be taken not to give doses which are too large. In certain cases this has been done and they have been followed by disagreeable symptoms such as a severe occipital headache and an anginal pain in the chest. The face becomes cyanosed, and the vision blurred, and the blood-pressure drops very rapidly. The usual dose to employ is from 0.3 to 0.5 mg., by subcutaneous injection.

Histamine has also been used for the determination of the velocity of the circulation. The time required for 0.1 mg. injected into the vein of the arm or leg to reach the superficial vessels of the face (where its arrival is heralded by flushing) is noted.

The appearance of the typical wheal at the site of injection has been used to determine the level of circulatory competency and to detect neurological disturbances.

Histamine has also been used in the treatment of the so-called "histamine" headache, and of allergic manifestations but the rationale for its use in these conditions and its value are questionable. The drug has also been administered by iontophoresis (*cf.* page 33) in peripheral vascular disease, and in rheumatoid arthritis.

Preparations

U. S. P.

Histamine Phosphas, histamine phosphate, $C_5H_9N_3.2H_3PO_4$, colorless crystals soluble in water. Dose, 0.3 mg., subcutaneously.

Injectio Histaminæ Phosphatis, a sterile solution of histamine phosphate in water for injection. Dose, 0.3 mg., intramuscularly.

Histaminæ Phosphas Acidus, histamine acid phosphate, the di-acid phosphate of histamine, 4-β-aminoethylglyoxaline. Dose, subcutaneously, 0.0005 to 0.001 gram.

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H. DRUGS OF INTERNAL SECRETION

One of the great advances in therapeutics of recent years has been the introduction of a number of effective agents derived from the glands of internal secretion. The hormones, as these active principles are designated, are extracted from the glands of animals, or prepared synthetically. In some cases chemical substances have been prepared which resemble the natural product and are used in the place of the naturally occurring derivatives.

The hormones resemble in many respects the vitamins discussed in the next section. They are effective in relatively minute amounts, and probably take part in the basic enzyme systems necessary for the normal functioning of the organism. As in the case of the vitamins, a deficiency of the hormones leads to widespread dysfunction in many of the organs and tissues.

The hormones vary in their **chemical constitution.** Some, like those derived from the pituitary and pancreas, are protein in nature. The adrenal and sex hormones are steroids in composition. As prepared from animal tissues, the extracts derived are not only frequently contaminated by extraneous materials but consist at times of break-down products derived from the naturally occurring hormones. The latter manifest only in part the action of the original physiological principle occurring in the natural state.

Except in the case of the thyroid, in which simple desiccation of the gland yields a therapeutically active product, the dry glandular materials are of no therapeutic value, although much used in times past. A series of complex chemical processes are necessary in order to concentrate the minute amounts of hormone present in the gland, and to effect a sufficient degree of purification to avoid toxicity in the final product. The potency of the extract thus obtained must, in most cases, be determined by biological assay, preferably by testing on animals from which the appropriate endocrine organ has been removed, in order to test their potency as substitution therapy. In addition to the hormonal products themselves certain related compounds prepared synthetically, are found to be of therapeutic value and because of their ready availability are often used instead of the naturally occurring

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hormone. Desoxycorticosterone, dihydrotachysterol and diethylstilbestrol belong to this group. In addition, a knowledge of the action of various hormones in the body has led to the adoption of supplementary procedures, for example, the administration of sodium chloride in adrenal cortical insufficiency or calcium salts in hypoparathyroidism, which are of great practical therapeutic importance.

The **method** of **administration** of the hormones varies depending largely on their chemical nature. Some are proteins and hence being reduced to their constituent amino-acids in the gastro-intestinal tract, must be administered parenterally. Others although active orally, are for greater therapeutic effectiveness nevertheless injected. Derivatives of the hormones are frequently utilized which unlike the hormone itself are effective orally. In other cases *sub-lingual* administration is effective presumably because when absorbed from this route inactivation by the liver is less than when absorption occurs from the intestinal tract.

The hormones normally are liberated into the circulation at a constant rate or at least in consistence with the demands of the organism. Intermittent administration thus fails to duplicate the condition occurring naturally in the body. To overcome this deficiency, slowly liberated compounds of certain hormones have been prepared and as in the case of protamine insulin or testosterone propionate have permitted better substitution therapy than is obtainable with insulin or testosterone alone. The implantation of relatively insoluble **pellets** of the hormone also permits not only a more efficient utilization but also avoids the necessity of frequent administration of certain hormones. This procedure has been found useful in treating certain chronic conditions in which replacement therapy over a long period of time is desirable.

The hormones like other medicaments attain their highest concentration at the point of application. Hence **topical** application is utilized when one desires a local effect, for example, the use of vaginal suppositories containing estrogenic hormone to induce stimulation of the vaginal tissues. In this way, moreover, one avoids to some effect the undesirable systemic effects of the hormone which are induced when it is administered parenterally.

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I. ANTERIOR LOBE OF THE PITUITARY BODY

The pituitary body or hypophysis is a compound organ comprising in the mammal four distinct parts: (1) an anterior or glandular lobe; (2) a posterior or neural lobe attached by a stalk which connects it to the mid-brain; (3) a pars tuberalis present as a collar of tissue surrounding the stalk; and (4) the pars intermedia which is vestigial in the mammal but assumes an important rôle in the lower vertebrates. Nothing is known concerning the function of the pars tuberalis. The other

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three components of the gland appear to function independently and will be considered separately.

The earliest ideas regarding the **function** of the anterior lobe came from the association of clinical disorders with pathological findings. Gigantism and acromegaly were correctly interpreted as being due to excessive secretion of the anterior lobe in the period of active growth and adult life, respectively. Deficiency was held to be responsible for adiposogenital dystrophy. The development of modern methods of surgical removal, however, has made possible the demonstration that the latter syndrome is due to injury of the hypothalamus although the lesion responsible for this disorder may ultimately also disturb the function of the anterior lobe of the pituitary. Removal of the anterior lobe results in almost complete cessation of growth in young animals, and loss of weight and general cachexia in the adult. There is a failure of the reproductive and general endocrine activity with atrophy of the genital system, endocrine organs, epithelial structures and tissues generally. The basal metabolism falls, the body temperature is subnormal and there is evidence of failure of the normal metabolic functions as a result of a deficiency in the utilization of protein, fat and carbohydrate. Interference with the last-named is particularly striking with a tendency to hypoglycemia which may be of sufficient degree to lead to a fatal outcome. The hypophysectomized animal is hypersensitive to external physical changes and to many drugs and easily falls prey to infections which prove rapidly fatal in the cachectic state of the organism.

The effects of a lack of the **growth hormone** are especially noticeable in young animals which, under these conditions, are unable to increase their skeletal dimensions or to maintain proper bodily growth. Certain types of human dwarfism have been ascribed to a similar deficiency of this hormone. On the other hand, an overproduction of the hormone is associated with gigantism, in which there is symmetrical overgrowth of the body, and with acromegaly, in which the overgrowth is not symmetrical. In both of these conditions the pituitary has been found to be the site of an eosinophilic-cell tumor.

When fresh glands are transplanted into hypophysectomized rats, there is a restoration of the normal rate of growth, sexual activity and normal histology of the genital system, thyroid, and adrenal cortex. These results cannot be produced by feeding the gland.

Next to its relation to growth, the relation of the anterior lobe of the hypophysis to the **reproductive system** has attracted most interest. In young normal female rats, mice, or rabbits, transplantation of anterior lobe or injection of certain extracts results in the rapid attainment of premature sexual maturity, as shown both by the behavior and by the development of ovaries, uterus, vagina, and other parts of the reproductive system. The uterine and vaginal changes are, however, indirect, being secondary to the primary effect on the gonads, since they do not occur in castrated animals. A similar acceleration of maturity can be produced in young males. When the sexual apparatus of young

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hypophysectomized animals is brought to maturity by such replacement therapy, the animals will mate and produce normal litters.

Clinically, hypophyseal insufficiency is a relatively uncommon condition. When occurring in the young, failure to grow and infantilism result but this is one of the rarest causes of dwarfism. In the adult, hypophyseal insufficiency gives rise to **Simmonds' disease** or pituitary cachexia. It results from atrophy of the gland, destruction of the gland by tumors within or near the sella turcica or as a result occasionally of infection or infarction of the gland. Insufficiency of the anterior lobe of the pituitary is not the cause of obesity, as was once believed, nor is it probably responsible for many other conditions for which it has been held responsible.

From a **pharmacological** standpoint, we are primarily interested in substitution therapy in conditions in which the normal secretion of the organ is deficient. This is readily attainable in the rodent, for when fresh glands are transplanted in hypophysectomized rats there is a restoration of the normal rate of growth, sexual activity and normal histology of the genital system, thyroid, and adrenal cortex. These results cannot be produced by feeding the gland.

When extracts of the anterior pituitary are fractionated it is possible to separate a number of principles which exert some specific function of the intact gland. These separations have in recent years led to the isolation in apparent pure form of various principles free of contamination by one another. To estimate their degree of purity several physicochemical procedures are utilized—electrophoretic analysis, observations in the analytical ultracentrifuge, and the determination of solubility curves in suitable solvents. The first procedure in particular as used in the moving boundary method of Tiselius has been applied widely in the study of pituitary extracts not only to determine the purity of a given extract but also of effect the separation of components in a mixture at least in sufficient amount for biological assay.

The following fractions have been separated from extracts of the anterior lobe of the pituitary:

A. Growth hormone, which maintains growth in the hypophysectomized animal and stimulates continued growth in the adult.

B. Gonadotrophic fractions. (1) Follicle stimulating hormone which stimulates the growth of the graafian follicles in the ovary and the spermatogenic tissue of the testis. (2) Luteinizing hormone, which stimulates the interstitial cells of the ovaries and testes, causing the formation of corpora lutea in the former and increased activity of the Leydig cells in the latter.

C. Thyrotrophic hormone, which stimulates the normal thyroid to overactivity.

D. Adrenotrophic hormone, which stimulates the adrenal cortex in the normal and prevents the regression in size of this organ following hypophysectomy.

E. Lactogenic hormone which induces lactation in species in which normally there is a certain amount of alveolar development of the breasts. This principle also stimulates growth and secretion in the crop-

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gland of the pigeon, and has a gonadotropic function. It is the only one of the anterior pituitary principles which has been obtained in crystalline form.

In addition, there is good evidence to indicate the existence of at least two principles that influence carbohydrate metabolism:

1. A pancreatrophic hormone which increases insulin secretion.
2. A diabetogenic hormone which either suppresses carbohydrate oxidation or increases carbohydrate formation (Young).

Other effects of pituitary extracts have suggested the existence of specific principles exerting effects on certain organs and metabolic functions in addition to those enumerated above. However, their existence has not been established definitely nor is their action in the organism clearly understood.

The existence of the above described fractions in extracts of pituitary glands is generally accepted as evidence that the gland normally elaborates these principles as separate hormones. However, this conclusion is not inevitable. It can be argued justifiably that the pituitary normally secretes a single hormone and that the separate effects seen in purified fractions represent probably only parts of the original hormone from which they are derived. A similar state of affairs exists in the case of the hormone of the posterior lobe described in the next section which recent evidence indicates also secretes a single hormone instead of two or more as previously believed.

Therapeutic Use.—Despite the vast amount of experimental work which has contributed to elucidate the physiology of the anterior lobe of the pituitary and the advances in our knowledge of the chemistry of extracts derived from the gland, the latter have found little application in medicine. The early enthusiasm for the use of growth hormone to stimulate growth has not been justified by subsequent clinical observation (Shelton). Equally discouraging results have followed the clinical trial of the gonadotrophic extracts to stimulate the ovaries or testes and to induce ovulation or spermatogenesis in cases where these functions are deficient. Nor have the other fractions of the pituitary been demonstrated to exert the desired reactions in the human as anticipated from their actions in the experimental animal.

The practical application of extracts of the anterior pituitary is still in an experimental stage of development. Their successful application must await further study and perhaps the availability of more highly purified and concentrated extracts which simulate in their action that of the normal glandular secretion.

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II. PITUITARY POSTERIOR LOBE

The extract of the pituitary body was shown by Oliver and Schaefer, in 1895, to exercise a pronounced effect upon non-striated muscle when it was injected intravenously; the anterior lobe proved devoid of this action. This effect on the walls of the blood-vessels caused vasoconstriction and a marked rise in blood-pressure. Dale, in 1906, first demonstrated the oxytocic action of the extract which led to its clinical use in stimulating the pregnant uterus. The third striking effect of the extract was shown by Van der Velde, in 1912, to be its capacity to inhibit the secretion of urine, that is, its antidiuretic action. In addition to these three diverse activities extracts of the posterior lobe exert a chromatophoric action which we now know originates in the pars intermedia of the hypophysis. Some (Abel) believed that the diverse actions of the posterior pituitary were due to the presence of a single hormone; others argued that there were at least two principles present one of which exerted the pressor and antidiuretic actions while the other manifested the oxytocic activity. This latter view seemed to be established when Kamm and his co-workers succeeded in separating the extract into two fractions: pitressin (vasopressin) which had the pressor and antidiuretic action and was devoid of any action on the uterus, and pitocin (oxytocin) which manifested the oxytocic action and was relatively free of action on the blood-vessels.

Chemistry.—Recent studies have established the unitary concept of the posterior pituitary hormone. Rosenfeld, by ultracentrifuging the juice obtained by pressing the fresh glands, showed that all the activities of the extract were probably associated with a single molecular species. Van Dyke and his co-workers established the concept with greater certainty by isolating a protein from frozen posterior lobes of cattle. This protein was demonstrated to be pure by its constant solubility and its behavior when ultracentrifuged or subjected to electrophoresis. The molecular weight of the protein is about 30,000 with an isoelectric point at pH 4.8. It has an unusually high content of sulfur (4.9 per cent) present almost entirely as cystine. The oxytocic, pressor and antidiuretic activities of the protein are present in the same ratio as in the dried gland. The activity of the purified hormone is approximately eighty times that of the international reference standard. It is unlikely that the protein isolated by Van Dyke and his colleagues has merely adsorbed several components of the gland. On the contrary it is very probable that the fractions obtained by previous workers represent breakdown products from the hormone molecule which accounts for certain differences observed between the action of the extract and the fractions derived from it.

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Physiology.—In connection with the pituitary gland, as also with certain of the other ductless glands, the question had from time to time been raised as to whether the active principles which are extracted from it are hormones which are elaborated in the gland and passed out into the body fluids to be carried to distant organs to perform a specific function, or whether they are merely potent chemical substances which are extracted through chemical manipulations but which may have no specific function in the body. An argument in favor of the former view has been furnished by the work of Haterius and Ferguson who carried out experiments in which the stalk of the pituitary was stimulated electrically at the same time as the uterine movements were being recorded. They found that when the stalk was stimulated there was an immediate increase in uterine movements, both increased frequency and increased amplitude, resembling in every way the changes produced by the injection of the oxytocic hormone itself. The response persisted after spinal transection, after cutting of the splanchnics and of the vagi, but was lost after the stalk of the gland was destroyed. A more potent argument in favor of the hormonal activity of the gland is the fact that its removal leads to diabetes insipidus which can be abolished by injections of extracts derived from the gland. That the gland normally plays a part in renal activity is also shown by cross-transfusion experiments with the isolated head of a dog. When the pituitary is removed from the head, diuresis is induced which is then abolished when transfusion from a head with an intact pituitary is resumed.

Action.—The administration by mouth of the dried gland or its extract is not attended by any obvious result, while the intravenous, subcutaneous or intramuscular injection of the aqueous extract causes pronounced effects in a number of organs, especially in those containing involuntary muscle. The effect of the extract differs to some extent in different species and is greatly modified by anesthesia. Its effect on the isolated organ may also be much different from that observed in the intact body. In the latter the effects of the hormone on the blood supply may modify its action on the involuntary muscle.

In general, the action of posterior pituitary extract is a summation of the effects of its oxytocic and pitressin fractions. That this should not always be true, however, is not unexpected if we accept the view outlined above that these fractions are derivatives of a single molecule.

Circulation.—When the extract is injected intravenously into anesthetized animals, the blood-pressure rises rather slowly and remains elevated for some time. The rise is usually preceded by an abrupt fall during which time the heart is accelerated, probably as a compensatory measure. The rise in pressure is due to constriction of the peripheral arterioles, as is shown by the lessened volume of the organs, and as this constriction occurs after the vasoconstrictor nerves have been divided and even after their connection with the muscular coats of the arterioles has been interrupted by ergotoxine, the pituitary substance must act directly on the muscle fiber. The rise in pressure under pituitary extract is smaller and less abrupt than that under epinephrine but is maintained longer. The constrictor action on the vessels may be shown by perfusing

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them with saline containing pituitary extract, when the venous outflow is at once reduced. All the arterioles examined appear to be constricted when thus perfused, but in the body they vary in their response, some being narrowed more than others and the renal vessels even being dilated. In the normal animal, as well as to a less degree in the etherized, the injection of pituitary extract produces a marked pallor of the skin and mucous membranes lasting from fifteen minutes to an hour or more. The capillaries are powerfully constricted.

The heart is generally slowed by the injection, and this partly through direct action on the cardiac muscle, and in smaller part from inhibitory action; the slight inhibitory stimulation probably arises partly from the increased blood-pressure flooding the brain and arousing the inhibitory center. But the extract also slows the excised heart perfused with Ringer's solution, which indicates that the muscle is directly affected. The sudden fall of blood-pressure which is often observed immediately after the injection appears to be due to cardiac action, spasm of the coronary vessels being mainly responsible for the cardiac weakness. The cardiac output is also greatly reduced with changes in the electrocardiogram characterized by alterations in its T-waves.

After the blood-pressure has returned to its normal height, a second injection of pituitary extract is found to have no effect or a much slighter one than the first, the vessel walls apparently having lost their power of response to the active principle. This phenomenon is known as *tachyphylaxis*. In man, the intravenous or subcutaneous injection of preparations of the posterior lobe is sometimes followed by an increase in blood-pressure, which may be maintained for a considerable period. However, in a certain number of persons the rise may be slight and in many cases, in place of an increase, there may be a very definite lowering of pressure. The diastolic pressure is usually raised, so that there is commonly a reduction in pulse pressure. Following the injection in man, there is also a decrease in pulse rate, in cardiac output, and in oxygen consumption. These changes last for a brief period, when they are replaced by a more prolonged rise in all three phenomena. The decreased cardiac output is probably only partly reflex in origin, and due in large part to a direct effect on the coronary arteries and myocardium (Grollman and Geiling).

Pitressin, in general, manifests actions similar to that of the whole extract on the cardiovascular system. However, pitocin also (Woodbury and Abreu) has cardiovascular actions which differ in different animal species. In the rabbit and cat this fraction lowers the arterial pressure and weakens the cardiac contraction; similar effects are observed in man although they are of short duration. In the fowl, the oxytocic fraction markedly lowers the blood-pressure, this phenomenon being utilized at times as a procedure for assaying oxytocic activity. This depressor effect of the oxytocic fraction is due to dilatation of the systemic arterioles.

Respiration.—The respiration is generally strengthened at first, but later becomes shallower and slower, and these phases may recur several times. After repeated injections of the extract, it ceases to have any

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effect. The center is acted on directly, the action beginning at the same time as that on the blood-pressure. In the rabbit and guinea pig the bronchial muscle is strongly contracted but this effect is probably due to histamine contamination of the pituitary preparation. Highly purified preparations are said to have no constrictor effect on the bronchi. In the unanesthetized animal the intravenous injection of the extract causes apnea alternating with periodic panting and marked acceleration of the respiration. These changes, which are ascribed to impairment of the circulation to the respiratory center through vaso-constriction, are much less marked in the etherized animal and also when it is given to the normal animal by the subcutaneous route.

The **Stomach** and **Intestine** are aroused to stronger contractions under pituitary extract. The tone of the intestine is increased and defecation soon follows in the case of the unanesthetized dog. The action on the intestine also occurs in man. In the dog the pressor factor seems to be more important in its effect upon the intestine than the oxytocic principle which exerts relatively little effect. Variation in technique and differences in reaction between different species of animals probably explain the many discordant results which have been reported in the study of this question (Larson). In cats which had been injected with thorium dioxide, rendering the colon opaque to the roentgen-rays, pitressin produced in certain cases a marked colonic contraction which reached its maximum in fifteen minutes. The animals differed in their susceptibility to the pitressin and negative results followed the use of the oxytocic principle. The bladder undergoes changes similar to those in the intestine.

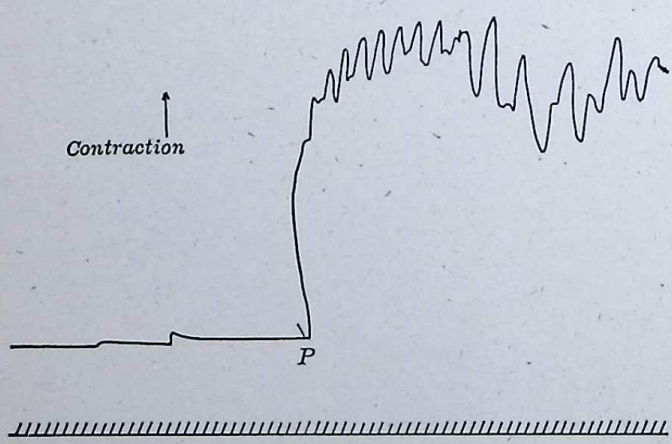

FIG. 49.—Contraction of the isolated uterus suspended in Ringer's solution; pituitary extract was added at *P*. (Dale.)

The isolated **Uterus**, submerged in a warm saline bath, contracts more strongly and relaxes less completely after pituitary extract (Fig. 49), and this change differs from that seen under epinephrine in that the stimulating action occurs in all animals, whether pregnant or not, and therefore cannot be attributed to an action on the nervous mechanism but must arise from a direct muscular effect. In the intact animal and in the human patient the action of pituitary extract on the uterus is

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not so simple, and its effect is apparently modified by various factors, such as the condition of the uterus itself, whether it is in the non-pregnant state or, if pregnant, whether in the early or late stage (see Fig. 50). Whether the organ is quiescent or actively contracting is important, as it responds much more strongly to pituitary if in the latter condition. The organ *in situ* would also be influenced by hormones from the ovaries and the effects of these will doubtless determine to some extent its reactivity to the oxytocic principle of the pituitary. For example, the uterus of a castrate, which is normally refractory to posterior pituitary extract can be sensitized by the prior administration of an estrogen. In general the uterus seems to be most reactive to pituitary in late pregnancy and during labor, so that preparations of the gland have to be given with caution in order to avoid tetanic contraction of the uterus, with suffocation of the child, or even rupture of the organ. The action on the uterus is more marked than the motor action on the alimentary tract.

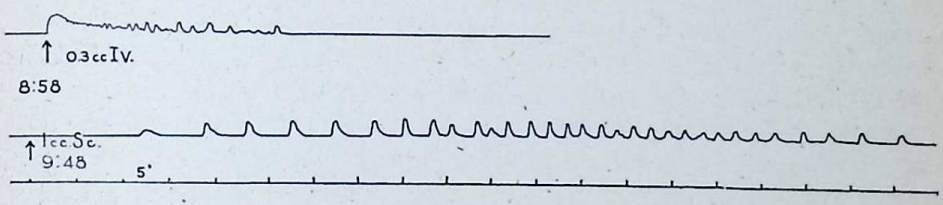

FIG. 50.—Effect of pituitary extract upon the human uterus. Tracings taken from a patient on the eighth postpartum day. A rubber balloon was placed in the uterine cavity and connected with a bellows recorder. Upper tracing shows the effect of 0.3 cc. of pituitary extract given intravenously. Lower tracing taken from the same patient 50 minutes later following administration of 1 cc. of pituitary extract subcutaneously. Time intervals, five minutes. (Gardner and Bradbury.)

Morgan has analyzed the effect of extracts of the pituitary gland upon the uteri of anesthetized rabbits, comparing the effect of the extract with that of its two components, as illustrated by pitressin and pitocin. The oxytocic principle caused a contraction of the uterus followed by augmented activity, while the contraction caused by the pressor principle was followed by a period of lessened activity which is accompanied by a fall in volume of the uterus due to a spasm of its vessels. The effect of the injection of the whole extract is the sum of the two components, the presence of the pressor principle being responsible for the late depression of activity sometimes seen. There is some question as to whether the oxytocic fraction exerts the same action on the intact human uterus as does the pituitary extract from which it is derived.

Melanophores.—When frogs are treated with pituitary extract, a distinct darkening of the skin is observed from dilation of the melanophores or pigment masses; this appears to be due to a direct action on the pigmented cells. The anterior lobe of the gland of most animals is apparently devoid of the substance which produces this effect as it is confined to the neuro-intermediate lobe. The melanophore-stimulating principle has been named *Intermedin*. The presence of this hormone in extracts of the posterior lobe of the pituitary is due to the fact that the

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pars intermedia from which it is derived is closely attached to the neural lobe and the combined tissues are used in the preparation of posterior pituitary extract. In animals in which the pars nervosa is entirely separate from the pars intermedia such as the chicken, porpoise, armadillo, or whale, extracts of the former manifest no action on the melanophores. In these species, extracts of the anterior lobe exert an action on the melanophores.

Boiling posterior pituitary extract with alkali results in the destruction of its pressor, oxytocic and antidiuretic actions. On the other hand, the chromatophoric activity of such extracts is actually enhanced by this procedure.

By means of tissue culture of the different portions of the pituitary gland, Geiling and Lewis obtained evidence that the melanophore expanding hormone is elaborated in the pars intermedia, but that this portion of the gland does not form the pressor hormone, as extracts of the pars intermedia tissue possess no blood-pressure raising property. The tissue cultures from the anterior lobe gave neither blood-pressure raising nor melanophore-expanding effects.

The **Pupil** appears to vary in its reaction and shows no very marked change as a general rule; in the excised eye of the frog some observers obtained dilatation, others contraction; in the rabbit contraction generally occurs from intravenous injection, dilatation from instillation.

Kidney.—One of the earlier observations was that pituitary administration to anesthetized animals was followed by a profuse secretion of urine. This is accompanied by an accelerated flow of blood through the kidney, while the amount of oxygen used in the organ is not increased. The period of diuresis in the rabbit, which lasts about one-half hour, is often preceded by a brief period of lessened flow of urine which has been ascribed to the action of the extract upon the ureters producing a constriction. It is doubtful if this action is of any importance, for in hydrated animals even minute doses of the extract prevent diuresis. Various explanations have been given for the diuresis which may follow the administration of the pituitary preparations. It seems clear that it is not due to a direct action of pituitary upon the kidney, and from the fact that the urine is rich in salts it is believed that the diuresis, in part at least, is in reality a saline diuresis, the increased fluid of the urine being necessary to eliminate the salts. An improved renal circulation is doubtless an important factor in bringing about the diuresis, as there is usually an increased renal blood flow and an increased kidney volume. A contraction of the efferent arterioles has also been found which would increase glomerular pressure and thus favor diuresis.

After the period of diuresis has passed off there usually follows a stage of diminished urinary flow which may last for a considerable time. In man and in unanesthetized animals diuresis is not induced and the effect of the extract is solely to lessen urinary flow. This antidiuretic effect is due to the stimulation of reabsorption of water in the thin portion of the loop of Henle and the terminal portion of the proximal convoluted tubules (Burgess, *et al.*). Denervation of the kidney does not prevent the reaction nor is it secondary to changes in blood flow through the organ. In addition to this effect on water absorption the hormone also decreases the reabsorption of salt.

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The antidiuretic effect of posterior pituitary extract is especially marked in cases of polyuria, notably in cases of diabetes insipidus. In this condition the urine is enormously increased, as much as 10 to 30 liters being passed in twenty-four hours or many times the normal amount; this is accompanied by intense thirst and large amounts of water are drunk. There is often some lesion in the neural lobe of the pituitary, the pathways connecting this lobe to the hypothalamus or in the hypothalamus itself. The hypodermic injection of pituitary extract reduces the urine to within ordinary limits, and by repeated injections this may be maintained but the diuresis returns as soon as the treatment is stopped (*cf.* Fig. 51).

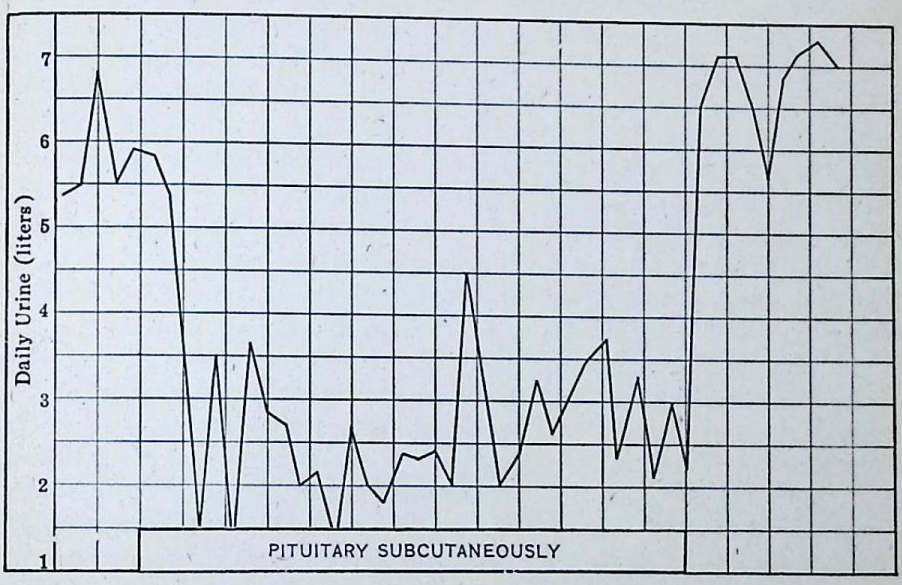

FIG. 51.—Urine in a case of diabetes insipidus in a child. The subcutaneous injection of pituitary solution, at first 0.25 cc. three times daily, later 0.05 cc. twice daily, reduced the urine from about 6 liters to 2.5 liters; the intake of fluid fell in the same proportion. (Christian.)

In frogs the injection of pituitary extracts produces a gain in weight as a result of the passage of water into the body through the skin (Boyd and Segal).

The administration of massive doses of pituitary extract to rabbits is followed by a marked anemia which reaches its highest development about the fifth day following the injection of the extract. According to Gilman and Goodman, this anemia is not due to a specific action of the pituitary, but rather is caused by water retention produced by the antidiuretic action of the drug. The lowered osmotic pressure of the serum presents an abnormal environment for the red cells and causes their destruction.

Milk-secretion.—One unique property of pituitary extract is its power of apparently increasing the secretion of the mammary glands. The rate of outflow may be increased as much as eighty times by an intravenous injection of pituitary extract and Schaefer states that even the glands of a non-pregnant cat may be induced to expel some serous fluid under its influence. However, pituitary extract does not actually increase the amount of milk formed, but merely causes its rapid expulsion by arousing the unstriated muscle of the gland to contract; this is not pre-

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vented by atropine, the muscle fibers being affected directly. While the secretion is increased immediately, the total amount of milk per day is not augmented in cows. In the human subject pituitary extract injected intramuscularly causes tingling in the breasts and then free secretion. The extract of the pituitary of birds and fishes is also a galactagogue in mammals.

The Central Nervous System does not seem to participate in the action of pituitary extract except after very large doses, which are followed by some somnolence and muscular weakness. The cerebrospinal fluid is increased, apparently from a direct action on the choroid plexus.

The action of pituitary extract is apparently a direct one on the terminal organs in each case and not on the nervous mechanism. The failure of a second injection to induce effects comparable to the original one has not been explained in any way. The most typical effects are obtained by the intravenous injection of the extract, but subcutaneous injection also elicits them in a less marked degree. Little or no effect follows the administration of the gland or its extracts by the mouth. A general action of the drug is also obtained from its application to the nasal mucous membrane. For this purpose a pledget of cotton moistened with a dilute solution is placed in the nasal cavity.

General Metabolism.—The administration of extracts of the pituitary is followed by hyperglycemia. While some hyperglycemia does follow the injection of the crude extract or of pitressin in rabbits, the dosage necessary is too high to be considered physiological. In dogs, on the other hand, mild states of hypoglycemia which have been produced by insulin can be abolished by the oxytocic hormone of the pituitary, while the pressor principle has no such action. Large doses of the oxytocic principle will not only remove the insulin hypoglycemia, but will also cause a condition of hyperglycemia (Ellsworth). However, the purified hormone isolated by Van Dyke and his collaborators exerted no effect on the blood sugar of rabbits and hence it is improbable that the hormone is of any significance in carbohydrate metabolism.

The pressor principle has also been shown to produce a fatty change in the liver of certain animals, an action which is almost absent from the oxytocic fraction.

Further changes in metabolism following the injection of the pressor principle into unanesthetized animals are indicated by the arterial hue of the blood returning from the muscles during the early period following the administration of the drug. The lessened oxygen consumption is accompanied by an increase in lactic acid in the blood, together with a lowered carbon dioxide tension. This period, during which the tissue is apparently not taking up oxygen and occurring when the output of the heart is lowered, is followed by the period of recovery when the conditions are reversed, the blood being of a dark color, with increased use of oxygen in the tissues, with a rising production of carbon dioxide, and return of lactic acid to its normal level. Whether these changes are brought about through an action on the cells or through the vascular changes produced by the drug is unknown. The former would be most probable.

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The **Excretion** of the pituitary principle appears to be slow and to be performed by the kidney. Most of the hormone is destroyed in the tissues, only a small portion appearing in the urine. Some experimental work seemed to suggest the presence of pituitary secretion in the cerebrospinal fluid, but the oxytocic effect produced by this fluid has more recently been shown to be due to its calcium content.

Therapeutic Uses.—Pituitary preparations are used extensively in obstetrics to arouse or to strengthen the contractions of the uterus. However, its use is attended with certain serious dangers which militate against its general use. The effects come on in from two to three minutes after subcutaneous or intramuscular administration of the extract, reach their maximum strength quickly and begin to decline in ten to fifteen minutes. The usual effect is to increase the number and the strength of the individual contractions but sometimes a tetanic spasm of the muscle supervenes which may be a source of danger to the life of the child.

The drug may be used in the second stage of labor in case there is no contraindication such as a disproportion between the size of the pelvis and that of the fetus and if the cervix is fully dilated. In case the cervix is not dilated or if there is some obstruction of delivery the strong contractions of the organ which would be caused by the extract might result in rupture of the uterus with death of the child and grave danger to the mother.

The extract is also very useful following the delivery of the child when there is postpartum hemorrhage due to an atonic condition of the uterus. When used in such cases in full doses it usually proves very effective. When it is given during the course of labor, however, it should be used in very small doses which may be repeated at intervals if necessary. The small divided doses lessen the likelihood of spasm of the uterus with danger of rupture of the organ or laceration of the other soft tissue. Pituitary is also used to some extent to induce labor during the last few weeks of pregnancy.

The extract has been used to increase the blood-pressure, especially in shock, but its use for this purpose is irrational since the extract does not counteract the peripheral vasodilatation characteristic of shock and tends, if anything, to aggravate the condition. In the normal human, injection of posterior pituitary extract may occasionally induce a shock-like state.

In atony of the intestines such as may occur following surgical operations or as a complication of some of the acute infections, it has been used at times with success. Other measures are, however, usually preferred for this condition.

An important use of posterior pituitary extract is in diabetes insipidus where the polyuria can be controlled by the use of the drug which acts as a substitution therapy for the deficiency induced by failure of the gland to secrete its hormone. The relief is only temporary, lasting only so long as the extract is being given. It may be administered in this condition by hypodermic or intramuscular injection once or more daily depending upon the severity of the disorder. Aside from the inconveni-

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ence of frequent injections, the parenteral administration often gives troublesome abdominal cramps and diarrhea. For this reason many prefer to administer the drug by insufflation of the dried powder. This latter method is satisfactory except for the local nasal irritation which it sometimes induces. Pitressin has also been used in the form of a tannate which is slowly absorbed and hence obviates the necessity of frequent injections. A single injection of this preparation every twenty-four to forty-eight hours, may adequately control the polyuria and polydipsia of patients with diabetes insipidus. Pituitary extract may also be given by the rectum but when given by this route its effect is very transitory. Administration of the extract by mouth is without value.

Preparations

Injectio Pituitarii Posterioris (U. S. P.), posterior pituitary injection, a sterile solution in water for injection prepared from the posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The potency is such that 0.1 cc. of the solution possesses an activity equivalent to one U. S. P. Posterior Pituitary Unit which is equivalent to 0.5 mg. of the U. S. P. Posterior Pituitary Reference Standard. Dose, 1 cc. intramuscularly.

Extractum Pituitarii Liquidum (B. P.). Dose, 0.2 to 0.5 mil.

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III. THYROID GLAND

The treatment of certain diseases by the administration of thyroid gland and its extracts is one of the most satisfactory examples of rational therapeutic progress, and the steps which led to its adoption may therefore be briefly mentioned. In 1882–3, Kocher and Reverdin published observations made on patients whose thyroids had been totally extirpated, and who had subsequently presented a series of symptoms

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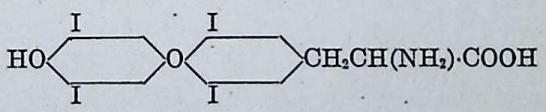
to which these observers gave the name of cachexia thyreopriva. They pointed out that this condition resembled in many of its features myxedema, a disease discovered by Gull some years before and associated with atrophy of the thyroid gland. These observations were confirmed by a number of authors, who removed the thyroids from animals, and induced cachexia in them. The next advance was the discovery that these symptoms in animals could be removed, or at any rate ameliorated, by grafting pieces of thyroid in the peritoneal cavity or subcutaneous tissue. Horsley suggested that myxedema should be treated in the same way, and Murray soon afterward introduced the treatment of this disease by the subcutaneous injection of thyroid juice. Even in his first case, the results were eminently satisfactory, but it was soon found that the same results could be obtained by administration by the stomach, and a large number of cases have now been recorded in which very favorable results, or even the complete disappearance of the symptoms has followed this medication. These include not only myxedematous patients, but also cases in which the thyroid was removed by surgical operation, or where its disease gave rise to symptoms. That the favorable results are due to the treatment is proved conclusively by the return of the symptoms when it is abandoned.

Chemistry.—The effect of the thyroid treatment could be explained only by the presence of some chemical principle, for the preparation of course contained no living cells. A globulin, thyreoglobulin, was extracted from the gland, which had the therapeutic action and gave the ordinary protein reactions but was characterized by containing a small percentage of iodine; Baumann's detection of this element in the thyroid gland was the first intimation that it existed in the tissues of the higher animals and man. In 1919 a crystalline substance was isolated from the gland by Kendall and named by him *Thyroxin*. By improving the method of isolation, Harrington succeeded in greatly increasing the yield of thyroxin to be obtained from the gland and showed that the substance is a tetra-iodo derivative of the hydroxyphenyl ether of tyrosine with an empirical formula of $C_{15}H_{11}O_4NI_4$ and a structural formula as follows:



The correctness of this view was later confirmed by synthesis of the product by himself and Barger. Basing his calculation upon the fresh gland, Harrington obtained a yield of thyroxin of 0.027 per cent, or 0.12 per cent of the dried gland. The synthetic thyroxin has been tested on patients and found to possess the effects upon the basal metabolism which are characteristic of the natural product and of the dried gland itself. However, per unit of iodine present in the compound thyroxin manifests less activity than does whole desiccated gland. This was originally attributed to the fact that its absorption from the gastrointestinal tract is erratic but the true explanation, as shown later, relies also on the fact that thyroxin is a derivative rather than the hormone

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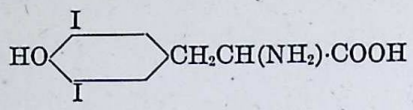
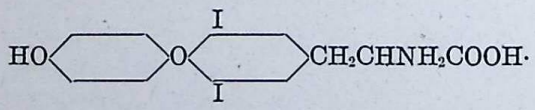
itself. Thyroxin is a white crystalline substance existing in the gland in protein combination.

A second compound containing iodine has also been isolated from the gland. This compound has been shown to be diiodotyrosine, possessing the formula.:



It will be seen that this compound is very closely related chemically to thyroxin, it being an intermediate product in the synthesis of the thyroxin in the thyroid. Previous to the isolation of this compound it had been suggested that thyroxin had probably been derived from tyrosine and now with the finding of this substance the relationship between tyrosine and thyroxin is established with diiodotyrosine as the intermediate product. Diiodotyrosine itself is only about 2 per cent as act ve as desiccated thyroid on the basis of their relative iodine contents. However, a combination of the compound with protein manifests considerable activity.

The simple incubation of protein with iodine results in the formation of an iodinated protein which has the qualitative action of thyroglobulin although it is much weaker in its action. From iodo-casein prepared in this way, crystalline racemic thyroxin has been isolated. It is assumed that iodine acts on the tyrosine present in the protein to give a diiodotyrosine and thyroxin protein combinations probably through the intermediate formation of diiodothyronine. The last named compound is the *p*-hydroxy-phenyl ether of diiodotyrosine or thyroxin minus its two iodine atoms in the 3^1, 5^1 positions. It has the formula:



The hormone of the thyroid gland according to the best available evidence is a protein complex of thyroxin, diidotyrosine and possibly diiodothyronine. This compound is referred to as thyroglobulin or iodothyroglobulin. It is unlikely that the thyroid hormone circulates in the organism in the form of so large a molecule which serves as the form in which the hormone is stored in the gland to be converted to a simpler polypeptid which is released into the blood stream.

Action.—The thyroid preparations and thyroxin often have little obvious effect in normal persons or animals unless given in what would be large doses for others; symptoms develop slowly and the maximum effect of a dose may not be reached for several days. The reason for this is that the administration of a hormone to the intact organism merely suppresses its production by the gland which normally elaborates it so that there is actually no excess circulating in the body. Undesirable effects are more liable to be induced by repeated doses than by a single large one. These symptoms are partly subjective and indefinite, such as headache, wandering pains, or general weakness, while others indicate

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circulatory changes, and consist of a feeling of fullness and congestion of the head, palpitation of the heart, and acceleration, sometimes weakness, of the pulse. Tremors in the arms and legs point to changes in the central nervous system, while loss of appetite and diarrhea indicate that the alimentary canal is not exempt from its influence. Perspiration is often complained of, especially in myxedema, and a rise of temperature also occurs frequently. The most striking effect in the majority of cases is a rapid loss of weight.

If to a completely myxedematous patient with a basal metabolism of about −30 a dose of 0.2 to 0.4 grams of desiccated thyroid is given, no subjective symptoms may be experienced for about twelve hours. After this time there may set in headache, loss of appetite, nausea and perhaps vomiting, pain in the back, legs and joints and an increase in pulse rate and in metabolism. The temperature rises to normal or perhaps to a little above normal. The skin becomes moist. These symptoms are most marked on the second day and the height of the metabolic curve is reached between the third and the tenth day. There is also a change in the appearance of the patient, the face becoming more expressive and the speech faster and more distinct. The period of discomfort may last one or two weeks, or in old cases, even longer. If the dose of dried thyroid has been smaller or if repeated small doses have been given the symptoms of discomfort are less marked but they are likely to last for a longer time. In any case, by the end of the second week the patient should have a normal metabolic rate and this is now maintained by the use of standardized thyroid preparation given daily.

In normal animals thyroid extract injected intravenously in large quantities accelerates the heart and lowers the blood-pressure slightly, and when given by the mouth repeatedly for several days, it may also cause some acceleration. This quickening of the heart has been attributed by some investigators to stimulation of the sympathetic nervous mechanism, by others to direct action on the heart; it does not seem to be due to any changes in the inhibitory apparatus. Hearts of animals which have been treated with thyroid so as to induce tachycardia, and are then removed from the body and perfused with Locke's solution will retain their rapid rate for a considerable period of time, even for hours.

Loss of flesh and thirst have been observed, even when the appetite is good and sufficient food and water are supplied. The urine is uniformly increased in amount. A number of observers have found that the continued administration to the animals of thyroid preparations in large amounts leads to diarrhea, muscular weakness, especially in the hind extremities, emaciation, gastro-enteritis, nephritis, and fatty degeneration of various organs. In other instances no such symptoms have been elicited, the animals remaining perfectly normal after prolonged treatment. Different species of animals vary greatly in their susceptibility to thyroid treatment, and this may explain some of the anomalous results recorded.

The **Metabolism** is changed by thyroid medication more uniformly than any other function, and this is its essential effect. All the nutritive processes seem to be accelerated. This may be observed in many indi-

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viduals in the rapid loss of weight, which often amounts to several pounds per week. Again, the amount of nitrogen in the urine is increased both in goiter and myxedema, and very often in apparently normal persons. More nitrogen is excreted in the urine frequently than is taken in the food, that is to say, the treatment leads to the destruction of the proteins of the tissues. If more nitrogenous food be given, however, this may be arrested, and in fact if large quantities of meat be taken, less nitrogen may be excreted than is taken in the food, so that although the patient is losing in weight, he may be actually increasing in nitrogenous tissue. The increase in the nitrogenous excretion is not stayed by the administration of carbohydrates and fats on the other hand, because the glycogenic function of the liver is disorganized by thyroid treatment. The increase in the nitrogen of the urine is accounted for almost entirely by the increase in the urea; the ammonia shows a very slight rise, while the uric acid and the creatinin remain almost unchanged; some creatin appears in the urine.

The calcium metabolism has also been shown to be modified, as the administration of thyroid preparations in addition to raising the general metabolism also increases the calcium output. In exophthalmic goiter there is a high calcium excretion which in extreme cases may lead to osteoporosis of the bones, while in myxedema the reverse is true. This effect is in large part if not entirely secondary to the effect on the gut, the increased motility of which in hyperthyroidism interferes with the absorption of calcium.

The other constituents of the tissues also are consumed more rapidly, and in fact the accelerated protein waste accounts for only about one-sixth of the loss of weight. The fats are reduced throughout the body, and the sugar metabolism undergoes modifications, which are shown in the disappearance of glycogen from the liver and not infrequently by the occurrence of glycosuria, either spontaneously or after the ingestion of quantities of sugar which would be oxidized completely in normal persons.

The acceleration of the metabolism is also shown by the increased amount of oxygen absorbed and of carbon dioxide exhaled under thyroid treatment. This has been noted in myxedema, goiter and obesity treated with thyroid, and has recently been shown to be the most regular effect of thyroxin; 1 mg. is sufficient to increase the basal metabolism by 2 to 3 per cent, while regular treatment with 2 mg. per day may raise it 20 to 30 per cent.

The removal of fluid from the body, perhaps the most potent factor in reducing the weight in these cases, is shown by diuresis, which occurs in myxedema especially. This diuresis has been ascribed to some specific action on the kidney, or to the changes in the circulation, but may perhaps be due to the increased excretion of urea and other urinary substances. Recently it has been shown that the administration of thyroxin is followed by mobilization of water and sodium chloride which, entering the blood stream, produces a high degree of hydremia and that the increase in urine is due to the ordinary changes in metabolism as the diuresis occurs early while the metabolism changes do not reach their

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maximum for some time. That the kidney is acted on in some cases is shown by the occasional appearance of albumin in the urine of patients treated with thyroid preparations. The phosphates excreted are increased in the same ratio as the nitrogen, and the increase is obviously due to the same cause, augmented protein waste.

A difference of opinion exists as to the site of action of thyroxin. According to Mansfield and his co-workers, the increase in metabolism is exerted on the periphery inasmuch as section of the cord has no effect on the metabolic changes and the inhibitory action of phenobarbital is probably a peripheral one. On the other hand, Issekutz and Dirner claim that mere section of the cord does not exclude a central action and that phenobarbital in the small amounts present in the blood in ordinary narcosis is not inhibitory to the action of thyroxin and they, therefore, believe the point of attack is on the central nervous system. The fact that thyroxin added to the medium in which tissue slices are suspended increases their oxygen consumption favors the first viewpoint.

It is believed that about 0.5 to 1 mg. of thyroxin undergoes destruction in the body normally each day and it has been calculated that on an average the normal human body contains 15 mg.; this amount of thyroxin given to a thyroidless patient will continue to act for one or two months, after which the previous condition recurs.

Kendall states that when injected into the blood about 40 per cent of thyroxin is excreted in the bile and 13 per cent in the urine within two days; there is thus little response to a single dose, but if the same total amount is given in repeated small doses, marked effects may be elicited. After thyroid preparations have been administered, iodine is found in the urine in the form of iodides, so that the thyroxin is evidently decomposed, at least in part, in the body.

The absence or atrophy of the thyroid gland in young animals or children arrests the growth both physical and mental, and treatment with thyroid extract accelerates the growth in many of these cases. In normal growing mammals, treatment with thyroid does not alter the general increase in size and weight greatly, but some organs, such as the heart, liver, suprarenals, kidney and pancreas grow more rapidly. In tadpoles fed with thyroid the increase in size is slowed or arrested, but the metamorphosis is much accelerated (Gudernatch), so that there results a number of small frogs, while the untreated controls are still large tadpoles; this accelerated development has been used to estimate the quantity of active principle in preparations of the gland. In other amphibia in which the metamorphosis is slower and less regular than in tadpoles, the results of thyroid treatment are even more striking.

When thyroid preparations are fed to fowls in fairly large doses the birds molt, losing their feathers within ten days, so that they may be almost featherless. The new feathers which come in are frequently different in color from the original in that many which were black or colored are replaced by white feathers, indicating a marked interference with pigment formation.

Therapeutic Uses.—Desiccated thyroid is used as a substitution therapy in several clinical conditions in which there is a deficiency of the normal secretion of the gland. The clinical manifestations of thyroid insufficiency vary depending upon the degree of the deficiency and the age of the

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patient. When there is a deficiency of the hormone in uterine life due to agenesis of the thyroid (sporadic cretinism) or to a deficiency of iodine available to the mother (endemic cretinism) irreparable damage to the nervous system results and the child ultimately presents the classical picture of the cretin (Fig. 52). A less complete degree of insufficiency occurring during childhood gives rise to retarded growth and mental development of a much less obvious degree. This condition is designated as *juvenile hypothyroidism*. In the adult, thyroid deficiency

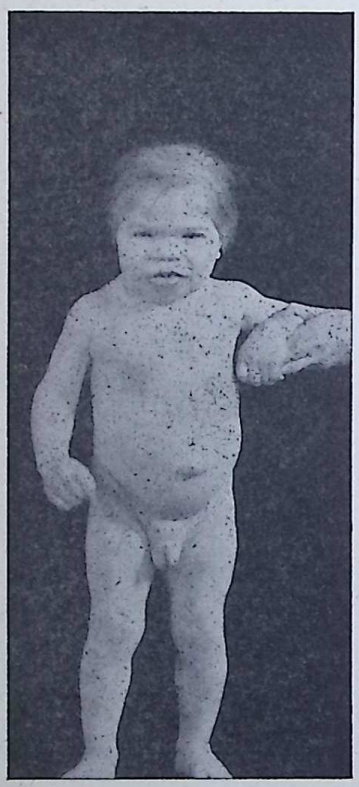

FIG. 52

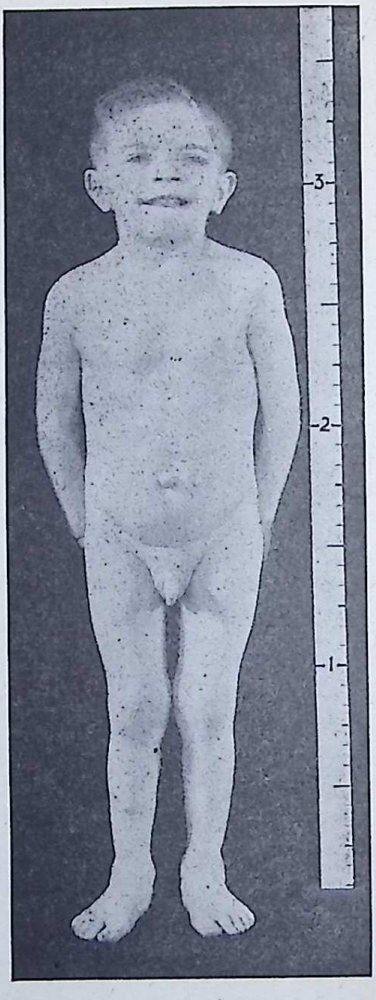

FIG. 53

FIGS. 52 and 53.—A case of sporadic cretinism. Fig. 52, before treatment, age thirteen years, height 36¼ inches. Fig. 53, after treatment with thyroid extract, seventeen months later, height 41½ inches. (Bronstein, *et al.*, Am. Jour. Med. Sci.)

if complete gives rise to a clinical syndrome first described by Gull in which there is a peculiar infiltration and thickening of the skin which he therefore designated as *myxedema*. However, partial deficiency may also occur in which the peculiar thickening of the skin is not pronounced but in which other evidences of thyroid deficiency are demonstrable. The latter condition is best designated simply as hypothyroidism, a term which includes also of course myxedema, juvenile hypothyroidism and cretinism.

Desiccated thyroid is useful as a substitute for the normal glandular

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secretion, but it must be used with care, especially if the heart is seriously affected, as the cardiac muscle may be unable to meet the requirements of the accelerated rhythm; several serious cases and one or two fatalities have been recorded in these conditions.

Desiccated thyroid is useful as a substitute for the normal glandular secretion in cases where the latter is wanting or deficient; thus in atrophy of the thyroid in adults (myxedema), after its extirpation (cachexia thyreopriva), and in its congenital absence or atrophy (sporadic cretinism) the most remarkable improvement follows its use, the patients from a condition of idiocy regaining practically normal intelligence (Fig. 53). It is of the first importance to commence the treatment as soon as the condition is recognized because unless the treatment is begun early no complete return to the normal is obtained, although improvement is observed even in neglected cases. The exact dose necessary to maintain a normal rate of metabolism must be determined for each case, but the average amount needed is from 30 to 120 mg. ($\frac{1}{2}$ to 2 gr.) of a standardized thyroid preparation daily. Changes in the size of the doses should not be made frequently as the full effects at a given dosage level are not manifest for three weeks. Changes in the dose are therefore made at three to four week intervals. After the correct dose is ascertained it is occasionally necessary to change it and it must be maintained in myxedema or cretinism throughout life.

The use of thyroid preparations in these conditions, in which the gland is atrophied, is readily understood. On the other hand, it may appear anomalous to employ it also in cases of enlargement of the gland (goiter). Yet great improvement is seen from thyroid treatment in many of these cases. In colloid goiter the gland is enlarged (hyperplasia), but this does not indicate an excessive formation of secretion, but the reverse; the gland hypertrophies in an effort to compensate for the poverty of iodine, and when the condition is treated with thyroid the hyperplasia lessens and the gland assumes its normal condition as far as the secretory epithelium is concerned, though it may remain enlarged through the presence of large colloid masses. Goiter does not require the permanent use of thyroid as a general rule; the treatment is carried on only until the gland is reduced in size.

The decrease in weight occurring in thyroid medication suggested its use in obesity, and it has been followed by some loss of weight in a certain number of cases, especially when accompanied by proper dietetic treatment. In many instances it has had little or no effect, however, and the initial encouraging action is seldom maintained when the treatment is continued, the daily loss of weight gradually becoming smaller until it ceases altogether. The amount of fat actually destroyed seems to be trifling, Magnus-Levy estimating that about one pound disappears in ten days, which is much less than can be got rid of by judicious exercise and an appropriate dietary. Besides, the continued use of thyroid in these cases is not altogether devoid of danger. Many of the antifat remedies put on the market contain thyroid extract and their continued use has led to serious symptoms in a number of cases.

Desiccated thyroid is also widely used in a number of other clinical

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conditions frequently without any rational basis and with questionable results. It is used widely by gynecologists in the treatment of various menstrual disturbances, sterility and abortion; by dermatologists for psoriasis and other chronic skin affections; and by internists for chronic fatigability and anemia of unknown origin, chronic obstipation, Ménière's disease, recurrent corneal ulcers, rheumatism, etc.

Preparations

Thyroideum (U. S. P., B. P.), thyroid, the cleaned, dried, and powdered thyroid gland obtained from domesticated animals that are used for food by man. Thyroid (U. S. P.) contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination. The B. P. requires only 0.09 to 0.11 per cent of iodine. Dose, U. S. P., 60 mg.; B. P., 0.03 to 0.3 gram.

Thyroxinum (U. S. P.), thyroxin, $C_{15}H_{11}I_4NO_4$, white needle-like crystals, insoluble in water but soluble in alkali. Dose, 0.5 mg.

Thyroxin Sodium (B. P.), the sodium salt of thyroxin, $C_{15}H_{10}O_4NI_4Na$. Dose, 0.1 to 1 mg. by intravenous injection.

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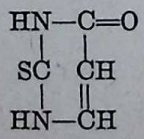
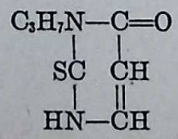
Thiouracil

The use of iodine to depress the activity of the thyroid gland in Graves' disease has been considered in an earlier chapter (page 73). Thiouracil also acts to overcome the symptoms of hyperthyroidism by interfering with the synthesis of the thyroid hormone and was introduced into clinical medicine for this purpose by Astwood in 1943. As seen in the accompanying formula thiouracil is 2-oxy-6-thiopyrimidine.



Thiouracil



Propylthiouracil

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Action.—A number of sulfur-containing compounds such as thiourea, the sulfonamides, thiocyanates, etc., had been previously shown to be goitrogenic, that is, to induce an enlargement of the thyroid gland and depress its action. This hyperplasia of the thyroid gland is apparently a compensatory mechanism comparable to that observed when a sub-optimal intake of iodine is provided or when other goitrogenic substances are ingested such as the leaves of the *Brassicaceæ* family (cabbage, cauliflower, broccoli), soy bean flour, etc. These act apparently by decreasing the availability of iodine, for their action is prevented by the simultaneous administration of this element. This supposition is borne out by the demonstration that thiourea *in vitro* protects tyrosine and casein against iodination (Miller, *et al.*). The thio compounds may thus prevent the synthesis of thyroid hormone in the gland by blocking the iodination of the precursors of the hormone. The enlargement of the gland is a secondary hypertrophy in response to the deficiency of the hormone in the body.

Thiouracil when administered to patients with thyrotoxicosis induces a lowering of the metabolic rate, which may return to normal, and concurrently induces a clinical remission of the disease. The prior administration of iodine prevents thiouracil from inducing its usual effects. In greatly enlarged glands also its effectiveness is not apparent for many weeks.

Toxicity.—The drawback to the clinical use of thiouracil has been its toxicity, approximately 13 per cent of all cases manifesting some adverse reaction to the drug. The most frequent and severe complications of thiouracil therapy are granulocytopenia, leukopenia, drug fever and dermatitis. Careful attention must be paid to the patient receiving thiouracil and the drug immediately withdrawn should any of these reactions appear.

Therapeutic Use.—Thiouracil is used clinically to induce a remission in thyrotoxicosis due to Graves' disease or toxic adenoma. It is possible by its preliminary administration to prepare the patient for subsequent surgery. The drug is usually administered in doses of 0.1 gram from four to six times a day until definite evidence of improvement is noted which usually occurs within a week or two when the dose is reduced to 0.1 gram once or twice a day.

Recently the propyl derivative of thiouracil has been tried with promising results. It is effective in smaller doses (25 mg. three times a day) and is possibly less toxic in effective doses than thiouracil.

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IV. PARATHYROID

Hanson and Collip in 1926 first prepared from the parathyroid glands of animals a potent extract containing an active principle or hormone

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which will relieve the symptoms of parathyroid tetany and in addition raise the blood calcium in a characteristic manner. In the tetany due to parathyroidectomy or to impaired function of these glands, animals have invariably a low blood calcium and an injection of the hormone will cause an increase in the calcium and at the same time relieve the symptoms. Animals which have had their parathyroids removed may be kept in perfect health by use of the extract but will exhibit tetany in a short time if its administration be stopped. If now a new injection be given, the animal will be restored to normal health in a very few hours.

Administered intravenously to normal dogs or to those having undergone parathyroidectomy, the curve of blood calcium rises, to reach its maximum between the fifth and the ninth hour, to return to normal in about twelve hours. When the hormone is given subcutaneously or intramuscularly the increase in the calcium appears somewhat later, beginning about the fourth hour. It reaches its maximum in from twelve to eighteen hours and returns to the previous level in from twenty to twenty-four hours. Associated with the rise in plasma calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the plasma content of the latter substance. If successive effective doses are given at fairly short intervals the effect is cumulative, resulting in a pyramiding of the effect of each dose upon the previous until a condition of hypercalcemia is produced with values even higher than 20 mg. per 100 cc. of blood. Such animals show signs of a profound intoxication which may end in coma and death. An early symptom of the hypercalcemia is vomiting, followed by diarrhea, weakness and some dyspnea. In fatal cases there are usually hemorrhages into the gastro-intestinal tract with vomiting of a bloody fluid, the passage of blood from the bowel, and anuria. Marked changes are produced in the blood in addition to the calcium alteration, there being an increase in its viscosity associated with a decrease in plasma volume; an increase in phosphates and in urea and non-protein nitrogen and a diminution in alkali reserve. At death the intestinal mucosa is found to be congested and the calcium content of certain tissues, especially of the heart and kidneys, is found to be greatly increased.

The effect of the parathyroid hormone is not limited to the blood calcium. The **inorganic phosphate** of the blood is affected to an equal degree being decreased by an excess and elevated by a deficiency of the circulating hormone. Normally the ratio of calcium excreted in the stool as compared to that in the urine is 4 to 1. In hyperparathyroidism excessive amounts of calcium and phosphate appear in the urine and there is a negative calcium balance; that is, the amount of this element which is excreted exceeds that absorbed from the gut. This excess calcium must come from the bones or from the soft tissues with the probability that it is the soft tissues which form the primary source and that they replenish themselves from the bones. Dogs may be maintained in a condition of mild hypercalcemia for weeks without any marked ill effects although during this time they must have suffered a considerable

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loss of calcium from their bones due to the excessive excretion of calcium salts.

Parathyroid **extracts** administered to young animals retard their growth and, given in excess, produce a resorption of bone, a decrease in osteoblasts and their change to fibrous tissue. These changes are followed by an increase in osteoclasts resulting in *osteitis fibrosa*. Continuous administration may result in a reversal of the process leading to the so-called "marble" bone (Burrows, Jaffe). It is probable that the hormone leads to resorption of bone and inhibits osteoblastic activity, the osteoblasts disappearing with the appearance of the osteoclasts.

The parathyroid glands are not only concerned with the increase in the calcium in the blood serum and in its application to the needs of the body, but also in maintaining the normal relationship between the calcium and phosphorus. There is in fact an inverse relationship between the blood calcium and the inorganic phosphate level. In hyperparathyroidism, the latter is decreased; in hypoparathyroidism, increased. The normal amount of calcium in the blood serum of man is about 10 mg. per 100 cc., while the average upper limit of inorganic phosphorus is about 5 mg. per 100 cc. in children and about 3.5 mg. per 100 cc. in the adult.

Clinically one observes hypoparathyroidism following thyroidectomy or when for any reason atrophy of the glands occurs. Hyperparathyroidism is associated with certain tumors of the glands. In cases of hypoparathyroidism associated with a lowered calcium content of the blood there is hyperexcitability of the nervous and muscular tissues which may progress to tetany, while in hyperparathyroidism there is depletion of the calcium content of the bones and an increased viscosity of the blood. Tumors of the parathyroids induce a variable picture. The outstanding symptoms may involve the neuromuscular system and rarely pronounced anemia may be the principal symptom of complaint. Most commonly, however, the bones are involved with generalized osteoporosis, bone cysts, pathological fractures and the deformities seen in *Von Recklinghausen's* disease of bone (*osteitis fibrosa cystica*). Another frequent manifestation of hyperparathyroidism is recurrent renal lithiasis, which is secondary to the excessive excretion of calcium phosphate in the urine.

Therapeutic Uses.—The parathyroid hormone is a potent agent capable of producing dangerous symptoms so that when administered to patients its effect should be carefully controlled by frequent determinations of the blood serum calcium. A serum content higher than 12 mg. is not desirable while levels higher than 15 mg. may be dangerous.

Parathyroid hormone is available in the form of an aqueous extract which is assayed by its capacity to elevate the blood calcium of normal dogs. One U. S. P. unit is one-hundredth of the amount of this extract required to raise the calcium level of 100 cc. of the blood serum 1 mg. within sixteen to eighteen hours. The hormone, being a protein, must be administered parenterally by the subcutaneous or intramuscular routes. Repeated administration results in an immunity or tolerance to the hormone. For this reason its use is limited to the early treatment

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of acute tetany where it is supplemented by the intravenous injection of calcium salts (gluconate or chloride). The immediate effects of the calcium, which are very transient, are followed by the slower results of the extract. In this way the tetany may be controlled for a few days until the dietary and other measures used in treating the chronic disorder are established.

Dihydrotachysterol is the drug of choice for the control of chronic hypocalcemia. This substance is a synthetic product formed by irradiating Ergosterol and is related structurally to synthetic vitamin D (see page 606), which also, when administered in large doses, causes an elevation of the blood calcium. Dihydrotachysterol (or A. T. 10 as it was originally designated) is administered orally and unlike parathyroid extract does not lose its effectiveness on continued use. It too, however, must be used with caution since overdosage leads to toxic levels of blood calcium. Doses of 5 to 15 mg. are administered daily until the blood serum calcium reaches normal after which the dose is adjusted to maintain this level. Dihydrotachysterol does not manifest its full effects for about a week to ten days. Hence the need for the intravenous calcium salts and parathyroid hormone during the first days of treatment of tetany.

A high calcium, low phosphorus, high vitamin D diet is also administered in chronic parathyroid insufficiency. Such dietary control alone suffices in mild cases to avoid tetany.

Parathyroid extract has been used also in lead poisoning as both lead and calcium are stored in the bones and both may be mobilized by the hormone. In some cases of lead poisoning treated there has been a marked increase in lead excreted, but the use of an acid-producing salt such as ammonium chloride is probably just as efficient and much safer. The extract has been tried as an aid in the healing of fractures, but it apparently has little or no influence here. It has been used in a number of other conditions in which there is abnormal calcification in an attempt to cause the solution of aberrant calciferous deposits. However, when so used, the calcium is released from the bones rather than from the sites involved. Dihydrotachysterol has also been used in pemphigus but its value in this condition is questionable.

Preparations

Injectio Parathyroidei (U. S. P.), parathyroid injection, a sterile solution in water of parathyroid extract. The available preparations contain usually 100 U. S. P. units per cc. Dose, 25 U. S. P. units by intramuscular injection.

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V. ADRENAL CORTEX

Brown-Séquard in 1856 showed experimentally that adrenalectomy invariably resulted in death in the course of a few days, a finding amply confirmed by later investigators. Furthermore, it has been shown that death is due to the removal of the cortex rather than the medullary portion of the gland. Various measures of treatment of adrenalectomized animals were successful in prolonging life for only a matter of days. However, in 1930, after numerous partially successful attempts, Swingle and Pfiffner first prepared active cortical extracts which restored the normal metabolism of moribund adrenalectomized animals, and on continued administration prolonged life for an indefinite period. Such characteristic postoperative effects as gastro-intestinal disturbances, muscular weakness and lethargy, lowered metabolism, lowered resistance to exposure to heat and cold, hypotension, anhydremia, hypoglycemia and increases in blood phosphate and non-protein nitrogen were successfully combated by the extract. Subsequent workers improved the methods of preparation of active extracts and isolated a number of crystalline substances.

Chemistry.—Our knowledge of the chemistry of the active principle of the adrenal cortex is still incomplete. Many crystalline substances belonging to the group of steroids have been isolated from cortical extracts. Most of these are inactive insofar as their capacity to replace the function of the gland in the adrenalectomized animal is concerned. Others exert a very definite effect in maintaining the life of adrenalectomized animals, or at least are capable of modifying one or another of the functions of the gland. For example, 17-hydroxycorticosterone and 11-dehydro-17-hydroxycorticosterone are active in restoring the defect in carbohydrate metabolism manifested in adrenal cortical insufficiency, but exert no effect on the sodium retention. Desoxycorticosterone, on the other hand, affects the sodium retention but exerts no effect on carbohydrate metabolism. However, no single compound whose structure has been determined equals in activity that of the extract from which it is obtained and it is probable that the potency of an extract is the summation of the activity of the several cortical steroids present, plus that of the hormone itself.

The production of cortin-like effects is not limited to products which have been isolated from the adrenal cortex, as somewhat similar effects are obtained by the use of other substances. Certain of the sex hormones, for example, also affect the sodium and potassium excretion, and thereby may have some effect in maintaining the health of adrenalectomized animals. In fact the administration of sodium chloride or glucose may also, under certain conditions substitute for the hormone

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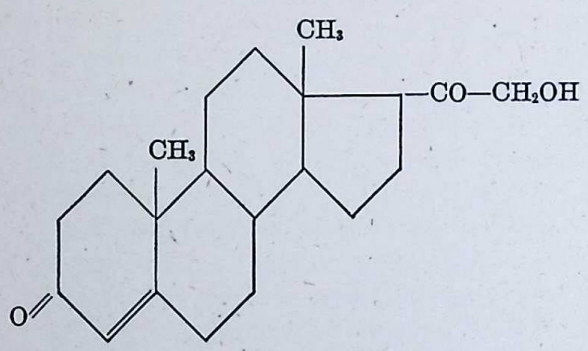
and overcome the effects of adrenal cortical insufficiency. However, in all of these cases, the replacement therapy is not complete and cannot be maintained indefinitely as is the case when the hormone itself is used.

Desoxycorticosterone.—The most important of the crystalline bodies derived from adrenal cortical extracts, is desoxycorticosterone isolated and synthesized by Reichstein. This compound because of its ready availability has assumed a place in the therapeutic management of adrenal cortical insufficiency. Desoxycorticosterone as seen in the accompanying formula is an allopregnane derivative related to progesterone (page 570). It is prepared commercially from stigmasterol, one of the sterols widely distributed in plants and prepared commercially from soya beans.



Desoxycorticosterone is a white crystalline substance insoluble in water. It is marketed in the form of its acetate dissolved in oil for intramuscular injection, in propylene glycol solution for sublingual administration or in the form of pellets for implantation. It is much less active per unit of weight than highly purified concentrates of adrenal cortical extracts nor does it completely substitute for the naturally occurring hormone, lacking, for example, the capacity to remedy the defect in carbohydrate metabolism manifested in adrenal insufficiency. It is thus incorrect to refer to desoxycorticosterone as the hormone of the gland. However, it is capable of prolonging the life of adrenalectomized animals. Because of its ready availability and the fact that the available extracts derived from glands are expensive and of low potency, desoxycorticosterone acetone is widely used in the treatment of adrenal cortical insufficiency in man.

Desoxycorticosterone differs also in its effects from concentrates of extracts derived from the adrenal glands in that it manifests certain toxic effects not exerted by the latter. When administered in excessive dosage in the normal as well as in adrenal insufficiency, it induces an abnormal retention of sodium and water in the body with edema, hypertension, and cardiac dilatation.

Action.—Various theories have been advanced to explain the function of the adrenal cortical hormone (sometimes called cortin or interrenalin). Swingle and his co-workers believe that it is responsible for the regulation and maintenance of the volume of the circulating blood, and that in its absence fluid is lost from the circulation by capillary transudation, the other effects following secondarily. They ascribe the lessened volume

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of blood to a loss of capillary tone with resulting dilatation, stasis and circulatory stagnation. According to them, therefore, the hormone is concerned with the maintenance of capillary tone and in the regulatory control of volume capacity of the circulatory system. Britton and Silvette stress the fact that hormone is necessary for normal carbohydrate metabolism and believe that hypoglycemia and a marked decrease of muscle and liver glycogen results in the characteristic picture of adrenal cortical insufficiency. On the other hand, due to the widespread physiological changes in this condition and a suggested relation to gonadal function, Hartman and his associates prefer to characterize it as a general metabolic hormone.

The cortical hormone is involved in the metabolism of sodium chloride; after adrenalectomy the rate of sodium excretion through the kidney is increased with a resulting decline in concentration of sodium, chloride, and bicarbonate in the blood serum. With the loss of sodium there is an increased loss of water, leading to a condition of dehydration and lessened blood volume, a lessened rate of blood flow and essentially what amounts to a state of shock. This disturbance in sodium metabolism is also seen in patients with Addison's disease, both in the effects of the withdrawal of an adequate amount of salt and in the beneficial effects of adding it to the diet. Wilder, Power and Cutler have shown that adrenalectomized dogs excrete excessive amounts of sodium and chloride and retain potassium, and that the administration of potassium will provoke an increased excretion of sodium and chloride and precipitate adrenal crisis. The average value of sodium in the plasma in Addison's disease is lower than that for normal subjects and the same is true for plasma chloride. The urinary sodium and chloride is considerably increased over the normal, a condition which is all the more remarkable in view of the lowered concentration of these substances in the blood.

None of the above mentioned theories will adequately account for the deficiencies observed in adrenal insufficiency. It is most likely that the hormone is essential for some very basic reaction in the organism and that in its absence many physiological mechanisms are rendered abnormal. By remedying one or another of these deficiencies, it is possible, according to this view, to compensate only in part for the hormonal deficiency and not entirely as would be the case if this were the fundamental deficiency involved. Confirmatory of this view is the fact that administration of saline will often revive animals and human patients in a state of shock secondary to the loss of blood volume, and administration of glucose will do the same where hypoglycemia is the presenting symptom. However, neither of these substances will indefinitely replace the hormone.

Grollman has shown that while cortical extracts will replace the hypoglycemia of adrenalectomized animals and maintain a normal level of carbohydrate, these extracts do not induce hyperglycemia in normal animals as is the case following the injection of certain of the steroids isolated from adrenal extracts.

In connection with the weakness and fatigability so characteristic of

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Addison's disease, Missiuro, Dill and Edwards have studied the effect of cortical extracts upon the performance of work in the normal human subject. They found that small doses had little effect in resting subjects, but that the efficiency of the performance of easy walking was increased for some days after the period of injection. The most characteristic change seen in severe work was the earlier return to normal of the blood-pressure. This was true of both systolic and diastolic pressures.

Unlike certain other hormones there is no evidence to indicate that the adrenal cortical hormone is toxic when administered in moderate overdosage, the excess being apparently excreted in the urine. This is not true of desoxycorticosterone. The pathological changes in the reproductive system observed in the so-called adrenogenital syndrome is apparently due to the elaboration by the gland in this disorder of androgenic compounds and not of an excess of the normal hormone.

Therapeutic Uses.—The pathological involvement of the adrenal glands in Addison's disease and the similarity of this syndrome to the findings following experimental adrenalectomy have led to the use of adrenal cortical extracts as well as the other substances found to be of value in prolonging the life of adrenalectomized animals in the treatment of this condition. Beneficial results have been produced in seriously affected patients and a definite prolongation of life has been reported as a result of such treatment. Ideally it would be desirable to treat the disease by the liberal use of the naturally occurring hormone present in adrenal cortical extracts. However, although several of these are available commercially, their expensiveness and the fact that they contain only small amounts of the hormone renders their wide use impracticable. For this reason except in the acute stages of the disease as in the so-called Addisonian crisis where liberal amounts (50 to 100 cc.) of the extract are administered intravenously, one must rely upon the use of sodium salts and desoxycorticosterone in the treatment of the chronic stage of the disease.

One of the chief deficiencies suffered by the patient with Addison's disease is the loss of sodium chloride from the body with the incidental loss of water, a decrease in blood volume and tissue fluids which may lead to shock and collapse. In addition there is an increase in the potassium and urea contents of the blood and sometimes a drop in the blood-sugar level sufficient to induce hypoglycemic reactions. The administration of sodium chloride either intravenously when necessary in crisis or orally in doses of 10 to 15 grams daily in chronic cases is thus an important adjuvant form of therapy. Since the loss of chloride from the body is less than that of base, it is preferable to give a mixture of two parts of sodium chloride to one of sodium bicarbonate or citrate (for example, 10 grams of sodium chloride plus 5 grams of sodium bicarbonate, daily). The exclusion of foods high in potassium content (for example, potatoes) and the use of a high carbohydrate diet is also advisable.

Where simple salt therapy as just outlined does not suffice to control adequately the symptoms, desoxycorticosterone is also administered. When this drug is used, attention must be given to avoid the toxic

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effects already noted which may prove fatal to the patient. One plan of treatment (Thorn) is to start with 6 to 8 grams of sodium chloride daily and 1 to 5 mg. of desoxycorticosterone acetate intramuscularly once daily, depending upon the severity of the case. The dose is then adjusted to the requirement of the patient. A weight gain of more than 0.3 kg. daily is indicative of the accumulation of edema fluid and hence of overdosage. A rise in blood-pressure above normal is also evidence of beginning toxicity.

Desoxycorticosterone may also be implanted in the form of pellets but before this is done careful metabolic studies are necessary to determine the number of pellets and the daily salt intake required.

In patients who respond well to the injection of potent cortical extracts or other forms of therapy, there is a disappearance of anorexia and vomiting and the development of a feeling of hunger. There is an increase in energy and relief from fatigue, and improvement in sleep, an apparent decrease in pigmentation, and a gain in weight. There is an elevation of body temperature, some elevation of blood-pressure, and in general a greater or lesser degree of rehabilitation. Not all patients will respond equally well to the effects of the extract, as some will be suffering from some primary disease, possibly tuberculosis, to which the adrenal condition may be secondary. Then, too, irreparable damage may have taken place in other organs before the extract was administered. While, therefore, cortical extracts are often of great benefit in Addison's disease, each case is a separate problem and requires individual consideration, depending upon the severity of the symptoms and the existence of possible complications. In a certain number of failures the trouble may have been due to the use of a weak extract or to insufficient dosage of a potent preparation.

The extract has been tried in a number of other conditions such as pernicious vomiting, pemphigus, neurasthenia, asthma, and acute infections, such as diphtheria, but with little avail, and, indeed, a scientific basis for such uses is lacking. Its value in patients with severe burns, in surgical shock and in the *Waterhouse-Friderichsen Syndrome* is not proved, although in the last named condition its administration would appear to be rational.

Some success has attended the use of concentrated extracts administered orally. Such extracts when accompanied by adequate amounts of sodium chloride have been used to a limited extent for maintenance of patients, but unfortunately the available oral preparations are of relatively slight potency. Desoxycorticosterone is also effective orally in the adrenalectomized animal and may be used clinically by sublingual administration.

Adrenal Medulla.—Epinephrine or adrenaline is obtained from the medullary portion of the adrenal glands. Since the action of this substance is sympathomimetic, it is discussed under that heading (page 485).

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VI. INSULIN

In 1889, v. Mering and Minkowski showed that the removal of the pancreas in animals gave rise to symptoms identical with those of diabetes mellitus in man, and attempts were subsequently made to obtain an extract of pancreas which might be of benefit in this disease. Success was attained in 1922 at the hands of Banting and Best, who obtained a preparation which was named insulin, since it is derived from the Islands of Langerhans in the pancreas, and not from the general parenchyma of the gland.

Chemistry.—Insulin was first obtained in crystalline form by Abel and his co-workers in 1927 by adding dilute alkali to highly purified commercial extracts in a strongly buffered solution. Adaptations of this procedure make it possible to prepare the hormone in crystalline form on a commercial scale. Crystalline insulin is a typical protein. Cystine, tyrosine, leucine, proline and glutamic acid are present in amounts from 10 to 20 per cent each, while arginine, histidine, lysine, phenylalanine, threonine, leucine and serine have been found in smaller amounts. The total amount of sulfur (3.3 per cent) in the molecule probably exists in disulfide linkage as cystine. Prepared from various sources and by different methods, crystalline insulin has a constant potency of 24 units per mg., indicating that the active principle is the whole product rather than a smaller chemical group adsorbed on a protein-like molecule. Such preparations derived from different animal species are also immunologically identical (Wasserman and Mirsky).

Scott established the fact that crystals of insulin contain zinc and that the addition of a zinc salt to amorphous solutions of insulin aid greatly in the formation of insulin crystals. In the same manner it was found that salts of cobalt, cadmium and nickel had a similar effect,

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although the zinc salt was most effective. In this connection it is important to note that zinc is found normally in the pancreas. It is probable that the various metals form salts of insulin and the microscopic appearance of the crystals is the same no matter which metallic salt is used to aid crystallization. Zinc insulin crystals contain 0.45 to 0.9 per cent of zinc and have a potency of 22 insulin units per milligram. The crystals contain from 0.2 to 0.4 mg. of zinc per 1,000 units.

Studies carried out to determine the effect of the presence of the metal upon the action of the insulin showed that when measured by the effect upon mice, zinc insulin solutions showed only 40 per cent of their original activity when they contained 0.02 per cent of zinc chloride. With such solutions the onset of convulsions in the mice was much delayed, suggesting that the action of the insulin was perhaps not actually lessened but was only delayed. Experiments upon rabbits confirmed this view, as it was found that the level of the blood sugar was lowered very gradually and was still well below normal at the end of ten hours, as contrasted with the original insulin where the blood sugar was practically normal in ten hours. The symptoms of hypoglycemia, such as convulsions, were also less marked, but the total glucose metabolized was approximately the same with the two solutions. Insulin is destroyed by pepsin as well as by trypsin and it is very readily precipitated in a state of adsorption when any of the protein precipitants are used. It is soluble in 80 per cent but not in 95 per cent alcohol. It is rapidly destroyed by alkali, but is more stable in acid solution. Insulin proper is found only in vertebrates including several varieties of fishes where the islets are present as separate bodies distinct from the acinar tissue of the pancreas. The claim that a similar substance (glucokinin) exists in plants is not correct. The hypoglycemic effects of the latter substances result from their toxic effects on the liver. They should obviously, therefore, never be used in treatment as substitutes for insulin.

Action.—Insulin has no apparent effects when given by the mouth, since it is destroyed by the digestive ferments. Injected subcutaneously in the rabbit, it causes a remarkable fall in the sugar of the blood from the normal of 0.12 per cent to 0.05 or 0.03 or less. When only 0.04 to 0.05 per cent of glucose is present, the animal becomes restless, and soon clonic convulsions with rotation of the body set in, resembling the convulsions under cocaine. The respiratory quotient rises, indicating an increase in the consumption of sugar. The convulsions can be arrested at once by the injection of glucose, so that they are obviously due to its deficiency in the blood and not to any direct action of insulin on the nervous centers.

Not only the sugar of the blood and tissues is destroyed, but the glycogen of the liver and muscles is drawn upon and may disappear when the convulsive stage is reached.

In diabetic animals and patients, the injection of insulin is followed by a rapid fall in the sugar of the blood, the disappearance of glucose and of acetone bodies from the urine, and general improvement in the symptoms of the disease. There is an increase in weight and in strength,

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a lessened polyuria and a diminished thirst. The dryness of the hair disappears and skin infections clear up. In man a healthy appetite returns and the mental attitude of the patient improves wonderfully. Most patients can return to work and in place of depression and despair there is mental alertness and a feeling of cheerfulness and of hope. As the insulin is consumed in the tissues, the symptoms return, and in order to maintain the normal condition a new injection is necessary. After a large injection, symptoms due to hypoglycemia are seen in man as in the rabbit, the severity of the symptoms in man depending upon the extent to which the blood sugar has been lowered. With a sugar content of about 0.08 per cent the patient may experience a vague sense of uneasiness and nervousness with a feeling of impending danger. There is an increase in pulse-rate, dilatation of the pupil, and a mask-like appearance of the face. With a blood sugar of 0.055 to 0.07 per cent there may be a feeling of anxiety and faintness, profuse sweating and incoördination. If the sugar is reduced still more (below 0.04 per cent) there is aphasia, disorientation, delusions and mental confusion and possibly coma and death. The symptoms due to hypoglycemia are rapidly relieved by the administration of glucose given by mouth, or if necessary by intravenous injection. Epinephrine is often effective in an emergency but its action is not so certain as it depends for its effects upon the supply of glycogen in the liver and as this may be present in only small amounts it is well to give glucose at the same time the epinephrine is administered. In the less severe symptoms due to hypoglycemia milder measures are usually sufficient. Frequently one-half an orange will be found effective, but if the condition has progressed so as to produce sweating, the orange is not sufficient and one or more tablespoonfuls of corn syrup may be indicated.

The **Mechanism** of **Action** of insulin is not known. It was originally believed that the hormone was essential for the utilization of carbohydrate and that in its absence this foodstuff could not be metabolized. However, following hepatectomy in the depancreatized animal, the blood sugar declines from its hyperglycemic level, indicating that even in the absence of insulin combustion of carbohydrate occurs. To what extent and how insulin deficiency interferes with the normal oxidation of carbohydrate is uncertain. It is evident, also, that in diabetes there is an excessive breakdown of protein and fat as well as a failure of normal deposition of glycogen in the muscles and liver. The excessive breakdown of protein results in the formation of glucose, which helps to maintain the hyperglycemic level of the blood and is also responsible for the rapid loss of weight often seen in the diabetic. The excessive oxidation of fat leads to flooding of the blood and tissues with ketone bodies, which also appear in the urine and give rise to the observed ketosis and acidosis.

Therapeutic Uses.—Insulin has provided one of the most dramatic therapeutic agents available to the physician. The use of insulin in diabetes has had brilliant results; replacing as it does the internal secretion of the pancreas as long as it is supplied. Unfortunately this neces-

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sitates subcutaneous injections, which must in the majority of cases be continued indefinitely.

Insulin is available in several forms for therapeutic use. The so-called "regular" insulin consists of an aqueous solution of amorphous insulin hydrochloride, containing traces of zinc and phenol or cresol as a preservative. Crystalline zinc insulin is also available and in its actions resembles that of "regular" insulin. Reactions due to the presence of foreign protein are rare, but when they occur following the use of "regular" insulin the crystalline compound should be utilized.

Insulin is injected into the subcutaneous tissue. In the case of regular insulin the injections are usually given about one-half hour before breakfast and then repeated if necessary before the noon and evening meals and, in case of need, a further small dose may be given at bedtime. The maximum effect from an injection is usually obtained in about an hour after the insulin has been given. The site of injection should be varied from time to time so as not to inject into any single area more often than once a month. If the injections are repeatedly given in one place tumefactions may result which predispose to infection and necrosis and, in any case, they interfere with proper absorption of the insulin. Also if the injections are scattered less insulin will be required.

A difficulty which is occasionally met with in the use of insulin and which is more serious than the occurrence of the localized tumefactions is the production of areas of so-called "insulin atrophies." These may appear at the sites of injections or quite frequently at some distance from the spots where the injections have been made. These areas are characterized by depressions of the skin with the disappearance of the subcutaneous fat and even of the muscular tissue also. Sometimes local recovery may take place in a year but again it may take a longer time and they may form a very annoying and disfigurng complication. The cause of these atrophies has not been explained nor is there any treatment known for them at the present time.

Protamine Insulin, Globin and **Histone Insulin** are modified forms in which insulin may be administered with advantage. In the use of "regular" or crystalline insulin by injections repeated two or three times daily, there are rather large fluctuations in the level of the blood sugar due to the rapid absorption of the insulin after it is administered and its subsequent disappearance from the blood. To avoid these pronounced variations in the blood-sugar level, efforts have been made to introduce the insulin into the body in some form in which its absorption would be retarded and in this way supply the body in a more gradual manner, thus tending to smooth out the large deflections in the sugar curve. Such modified insulins which are used clinically are Protamine, Globin and Histone Insulinates. These are formed by a union between insulin hydrochloride and protamine, derived from a species of trout, *Salmo iridius*, histone and globin prepared from hemoglobin, respectively. These combinations have a minimum solubility at about the reaction of blood serum. Globin insulin forms a clear solution; protamine insulin a turbid suspension. All are slowly broken down and the active insulin released over a longer period of time.

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The duration of the effect of protamine insulin is much greater than that of regular insulin, its maximum effects coming on between ten and forty-eight hours after its administration depending upon the dosage used. Globin and histone insulin are intermediate, as regards their duration of action between "regular" or crystalline and protamine insulin.

The prolongation of action manifested by the modified forms of insulin makes possible the control of the diabetic with fewer injections. By administering, for example, a single injection of a mixture of "regular" and protamine zinc insulin before breakfast, it is possible in some patients to maintain a relatively normal blood-sugar level throughout the day and avoid periods of hyperglycemia and hypoglycemia.

Zinc added to the various forms of insulin also greatly prolongs their hypoglycemic action. They are therefore marketed in combination with this metal.

The use of small doses of insulin has been suggested to improve the appetite in undernourished individuals and thus increase their food intake. However, it is possible that whatever improvement is made is due, in part at least, to psychic effects rather than to the insulin, and in any case it must be understood that insulin is merely an adjunct in the treatment. Insulin is also used as a convulsive in the treatment of certain psychiatric disorders.

Dosage.—Insulin is supplied in solution suitable for injection. The potency of the solution varies from 10 to 100 units per cc., the unit being the activity contained in 0.125 mg. of an international standard powder (8 units per mg.). No definite dosage can be given for insulin, as each case must be treated individually, but the average daily dose for diabetic patients is about 30 units (Joslin). In cases of diabetic coma or severe acidosis larger doses of insulin are indicated, accompanied by definite amounts of dextrose, so that the patient will not become hypoglycemic. Insulin is assayed by comparison with the standard either by the convulsive dose in mice or by the average blood sugar decrease in rabbits over a five-hour period following injection.

Preparations

Injectio Insulin (U. S. P.), insulin injection, an acqueous extract standardized so that each cc. contains 20, 40, 80 or 100 U. S. P. Insulin Units. The U. S. P., Zinc-Insulin Crystals, is used as a Reference Standard for the assay.

Insulinum (B. P.).

Injectio Insulini Protaminati cum Zinco (B. P.), injection of protamine zinc insulin. Dose, by injection and determined by physician in accordance with needs of patient.

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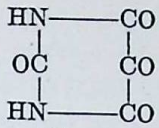
Alloxan

This substance which is derived by oxidation of uric acid is of interest in experimental physiology because of its remarkable property of inducing diabetes mellitus when administered to the experimental animal.



Alloxan

Following its injection there is a rise in the blood sugar which is followed by a reduction below normal and which in turn is again followed by hyperglycemia. The initial rise in blood sugar is probably due to a direct action of the drug on the liver. The hypoglycemia which follows the initial rise is not due to the liberation of insulin as formerly believed but is probably an extra-pancreatic effect due to the inability of the liver to produce glucose (Houssay, *et al.*). The drug causes destruction of the beta cells of the islets of Langerhans and thus gives permanent diabetes which is responsible for the final permanent rise in the blood sugar. The drug is toxic and undoubtedly affects other tissues than the liver and pancreas.

Alloxan has been used clinically in an attempt to depress the activity of the islet tissue in patients with carcinoma of the islet cells. Its toxicity, however, precludes its use in therapeutics for this purpose. The principal interest in the compound is its capacity to induce diabetes without necessitating pancreatectomy.

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VII. THE SEX HORMONES

The complicated processes which govern the manifestations peculiar to sex have been greatly clarified in recent years by the study of the hormones involved in reproduction.

The hormonal agents which act upon the reproductive system comprise two general groups: (1) the gonadotropins; and (2) the sex hormones. The former act directly on the gonads which are stimulated to secrete their own hormones which in turn affect the remainder of the reproductive system. The sex hormones proper are elaborated by the gonads and exert their effects on the accessory organs of reproduction as well as on the secondary sex characters.

The sex hormones may be divided into: (1) the female sex hormones which comprise the estrogenic and progestational hormones; and (2) the male sex hormone.

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1. The Gonadotropins

The gonadotropins (gonadotrophins) or gonadotropic hormones as they are also designated are of two general types: (1) those derived from the anterior lobe of the pituitary (*cf.* page 527); and (2) those elaborated by the chorionic tissue. These two general types of gonadotropins differ from one another in their action and the chorionic gonadotropins in turn vary in action depending upon the source from which they are derived.

The pituitary gonadotropins have been used to a much lesser extent in medicine than the chorionic gonadotropins which are much easier to prepare in a form suitable for injection. The presence of a chorionic gonadotropin in the urine of human pregnancy is responsible for the stimulation of the ovary which is the basis for various pregnancy tests. In the horse, the chorionic gonadotropin is not excreted in the urine but is present in high concentration in the blood serum. In certain respects this equine chorionic gonadotropin resembles in its action more closely the pituitary gonadotropin than does the gonadotropin of human pregnancy urine. It with human chorionic gonadotropin and pituitary gonadotropin constitute the three types of this hormone which are commercially available.

The gonadotropins are protein-like in nature and hence must be administered parenterally. They exert a stimulating effect on the gonads and hence are only effective if the gonads are present and capable of responding to stimulation. However, the stimulation induced is not of a simple nature nor does it duplicate the activity of the organ which occurs normally. Consequently the usefulness of the gonadotropins has been limited. It is doubtful for example if their administration in the human female results in simple ovulation such as occurs following their injection into the lower animals.

The principal use of gonadotropic extracts is in the treatment of **cryptorchidism.** In this condition, the injection of the hormone results in the descent of the testicles if no anatomical hindrance is present to prevent it. The chorionic gonadotropin of human pregnancy urine may be used for this purpose, being injected intramuscularly in doses of 200 to 500 international units two or three times per week for a period not exceeding six weeks. The international unit is 0.1 mg. of an arbitrarily accepted standard preparation maintained at the National Institute of Health.

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2. Female Sex Hormones

Since the early years of this century it has been known that the ovary and the corpus luteum, which appears following ovulation, secrete

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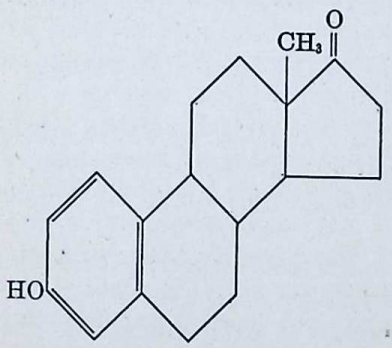
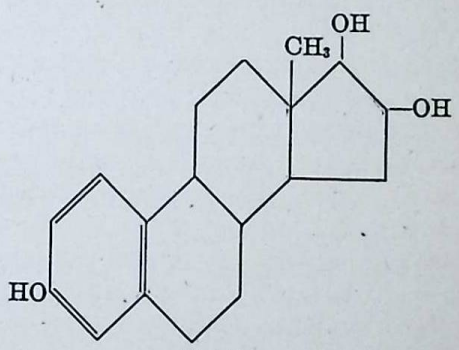
hormones which are essential for the normal development of the female reproductive system. These two distinct hormones, the estrogenic and progestational, constitute the female sex hormones. In 1922 Frank discovered that the *liquor folliculi* contained an active substance which produced effects similar to that of the ovary. Discovery of a method of determining the activity of the extracts through changes they produce in the vaginal mucous membrane of rodents furnished an important aid in the study of the problem. In 1929 the first crystalline estrogenic compound was isolated from urine by Doisy and his co-workers, and was shown to be identical with the active principle of *liquor folliculi.* In the years immediately following this important discovery other crystalline bodies were isolated from the urine of pregnancy or from ovarian tissue until a number of crystalline substances possessing estrogenic properties have been prepared.

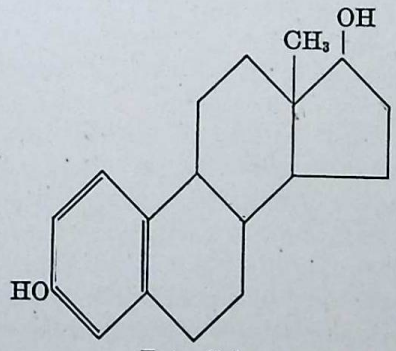
Chemistry.—The naturally occurring estrogenic substances are steroidal compounds. The principal ones occurring in the human are estrone or theelin, estriol and estradiol:



Estrone
$C_{18}H_{22}O_2$



Estriol
$C_{18}H_{24}O_3$



Estradiol
$C_{18}H_{24}O_2$

As shown in the accompanying formulæ these compounds possess an unsaturated ring, an angular methyl group at Carbon 12 and ketonic and hydroxyl groups in the 3, 16 and 17 positions of the perhydro-pentano-phenathrene nucleus. Since estradiol is the most potent of the naturally occurring estrogenic compounds it is believed to be the primary hormone. It is the dihydro-derivative of estrone into which

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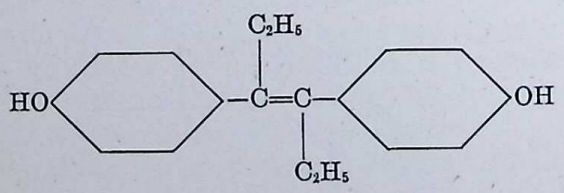
it is largely converted in the body. In addition to estrone, estriol also appears in human urine, both compounds being excreted largely as esters of glycuronic acid. The ovarian hormone, estradiol, exists in two isomeric forms—the *alpha* form, which is very potent, and the *beta*, which is almost inert. There is also a great difference in the relative activity of estrone and estriol, the former being much the more potent when injected, while the latter retains considerable activity even when administered orally.

The naturally occurring estrogenic compounds are derived principally from the urine of pregnant mares, which also contains a group of compounds—equilin, hippulin, equilenin, etc.—having two unsaturated rings as in naphthalene. An amorphous concentrate of the estrogen is marketed under various trade names in addition to the pure crystalline compounds—estrone, estriol and estradiol. Estrone is relatively inactive when administered orally. However, its sulfuric acid ester manifests activity following oral administration, and several preparations of amorphous concentrates of pregnancy urine or placental tissue, which consist principally of estrone sulfate, are prepared commercially for oral use.

Estriol is also available for clinical use in the form of its glycuronide which is active only when administered orally.

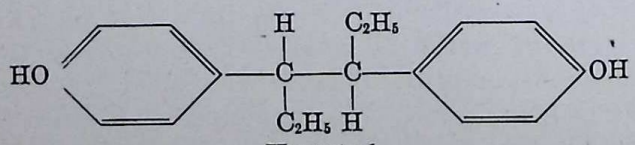
Estradiol is also marketed in the form of its benzoic acid ester in which form its activity is greatly enhanced. Its ethinyl derivative is also more active orally than is the parent substance, and this compound is available commercially.

Synthetic Estrogens.—The naturally occurring estrogenic substances have been displaced in therapeutics to a large extent by a number of cheaper synthetic compounds which exert the same biological effects as do the naturally occurring hormones. The most important of these synthetic compounds is diethylstilbestrol, the estrogenic activity of which was discovered by Dodds and his co-workers in 1936. This compound has the structure:



and is the diethyl derivative of paradihydroxystilbene.

Among the several derivatives of diethylstilbestrol which are also used clinically may be mentioned hexestrol, its dihydrogen derivative, benzestrol which contains an extra ethyl group, and monomestrol (mestibol), the monomethyl ether of diethylstilbestrol.



Hexestrol

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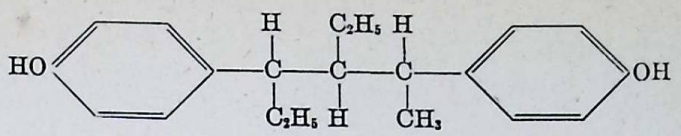
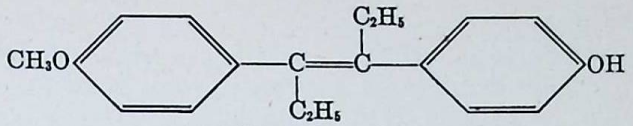


Benzestrol



Monomestrol

These derivatives of diethylstilbestrol are claimed to induce fewer side reactions but are also less potent than diethylstilbestrol and hence must be used in greater dosage to induce the same effects. Although superficially, diethylstilbestrol and its derivatives appear to bear little relationship to the naturally occurring estrogens, the former are converted in the body to the latter and hence exert the same actions. The cheapness with which they may be prepared and their effectiveness when administered orally gives the synthetic compounds an advantage for clinical use over the more expensive, naturally occurring compounds. They are available in tablet form for oral administration and also in solution for injection. However, only rarely is their parenteral administration indicated. In order to retard the rate of their absorption both the naturally occurring estrogens and the synthetic preparations are available in the forms of esters such as estradiol benzoate, diethylstilbestrol dipropionate, etc.

Physiology.—The estrogenic compounds act as stimulants to the accessory reproductive organs, producing hypertrophy of the uterus and cervix, and increased growth of the ducts of the mammary glands. They are responsible for the contractility of the uterus and for its sensitivity to oxytocics. Following castration the secondary reproductive organs atrophy and the rhythmic changes which characterize estrus cease. The injection of estrogenic compounds in the castrate will restore the atrophic organs to their normal state, as well as the rhythmic changes of the estrous cycle.

The estrogenic hormones are responsible for certain secondary sex characteristics in the female, such as the plumage markings of some birds and the sexual swellings of baboons and changes in the sexual skin of some of the monkeys. They will also produce certain female characteristics in the development of the gonads in male embryos.

The anterior lobe of the pituitary gland has a very important relation to the reproductive organs through the action of its gonad stimulating factor which promotes the growth and maturation of the ovarian follicles, which in turn secrete the estrogenic hormone. This hormone is probably produced by the cells of the theca interna, and through its action brings about the changes in the accessory reproductive organs which have been described. As the follicular hormone increases in quantity in the blood it in turn acts upon the anterior lobe of the pituitary, inhibiting the production of the gonad stimulating hormone and thereby lessening the stimulation of the follicles. There is thus pro-

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duced a regular cycle of alternate activity and quiescence on the part of the pituitary and of the ovarian follicles. In addition, the luteinizing hormone of the anterior lobe of the pituitary causes luteinization of the ovarian follicles with formation of the corpus luteum. This structure in addition to an estrogenic hormone secretes a hormone, progestin (later named progesterone) which acts upon the endometrium, inducing secretory changes preparatory to nidation. This hormone, which is described in greater detail later, is essential to nidation and also for the maintenance of pregnancy. It also stimulates the growth of the alveolar tissue of the mammary glands developed under the influence of the estrogenic hormones.

The progesterone is produced by the ovary only through the third month of gestation, after which time the **placenta** takes over its production. The placenta also produces large amounts of estrogenic hormone as well as the chorionic gonadotropin (*cf.* page 564), and hence this tissue assumes an important rôle in the elaboration of these sex hormones. Progesterone is found in the urine of pregnancy and during the corpus luteal phase of the cycle in the form of pregnandiol.

The **excretion** of estrogen in normal menstruating women is irregular, varying from day to day, although the curve of excretion shows two peaks during the normal menstrual cycle. The first of these is in the mid-interval, between the tenth and nineteenth days corresponding to the period of greatest follicular growth and ovulation. The second period is often inconstant in its appearance but usually occurs in the week prior to menstruation, and probably corresponds to some phase of corpus luteum activity. Following this peak there is a sharp fall in the curve of excretion followed under normal conditions by the onset of menstruation. During pregnancy there is a gradual rise in the level of excretion starting in the second half of the second month and continuing until the time of labor, after which the curve of excretion falls to normal in a few days.

Injected estrogen is almost entirely destroyed in the liver; only a very small amount, 3 to 12 per cent, can be recovered from the urine. Injected intravenously into dogs, 90 per cent of the amount disappears within a very few minutes.

Therapeutic Uses.—The estrogenic compounds find their main value in cases where there is a deficiency of these substances, as in cases where the ovaries have been removed or possibly at the time of the normal menopause. In some of these latter cases with vasomotor disturbances the results of the administration of estrogenic products have been favorable, but it must be recognized that in many such patients the psychic factor involved has not been ruled out and equally good results could have been and often are obtained by non-specific medication alone. Moreover, the value of the estrogenic compounds in the menopausal syndrome depends probably on the suppressive effects of this hormone on the pituitary rather than as a substitute for the normal ovarian deficiency. These substances have also been used in certain forms of amenorrhea and dysmenorrhea, but here, too, the results obtained are by no means convincing as proving their value in these

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conditions. Insofar as the first-mentioned condition is concerned, it may be said that from the physiological standpoint it would not be logical to expect them to be of value, for while estrogenic substances produce estrus in animals, the factors responsible for estrus and those producing menstruation are quite different. Thus the continued administration of estrogens results in building up of the endometrium. About a week or ten days after cessation of estrogenic therapy, bleeding occurs, but this does not constitute normal menstruation. Estrogen does not stimulate the ovary itself, but acts merely as a substitutional product which would be active only so long as it is administered and therefore would not be expected to establish a normal menstrual cycle.

In **gonorrheal vaginitis** of children the results of the administration of estrogenic substances have been more favorable. The improvement often seen is ascribed to changes produced in the vagina, the mucosa of which changes temporarily to the adult type with partial cornification. The secretions instead of being alkaline become acid and under these conditions the gonococci disappear. For this purpose estrogen is usually given in vaginal glycerin-gelatin suppositories. Some changes in the secondary sex organs may follow this treatment if it is too prolonged, but they usually subside when the treatment is stopped. However, in view of the effectiveness of the chemotherapeutic agents (sulfathiazole, penicillin) these have displaced the estrogens in the treatment of juvenile vaginitis. The estrogens are used in this condition in cases not responding to chemotherapy, or as an adjuvant in treatment.

Senile vaginitis is frequently benefited by the estrogenic hormone. The mucosa returns to the normal type seen during normal sex activity, and there is relief from the burning and pruritus common to the condition. In this condition the estrogens are best administered as vaginal suppositories. They are also used in eunuchoidism to stimulate growth of the breasts, being applied by inunction into the skin over the breasts.

Preparations

U. S. P.

Estronum, theelin, $C_{18}H_{22}O_2$. A crystalline estrogenic steroid obtained from the urine of pregnancy. Average dose, 1 mg. by intramuscular injection.

Estradiol. $C_{18}H_{24}O_2$. A crystalline steroid prepared by catalytic hydrogenation of estrone. Average dose, 0.2 mg.

Estradiolis Benzoas. The benzoate of alpha-estradiol. $C_{25}H_{28}O_3$. Dose, 1 mg. by intramuscular injection.

Diethylstilbestrol. A synthetic preparation. Average dose, 0.2 mg., orally.

Capsulæ Diethylstilbestrolis, diethylstilbestrol capsules. Average dose, 0.2 mg.

Injectio Diethylstilbestrolis, diethylstilbestrol injection. Average dose, intramuscularly, 0.2 mg.

Tabellæ Diethylstilbestrolis, diethylstilbestrol tablets. Average dose, 0.2 mg.

B. P.

Œstronum, œstrone, ketohydroxyœstrin, 3-hydroxy-17-keto-$\Delta^{1:3:5}$- œstratriene. Dose, orally or subcutaneously or intramuscularly, 0.0001 to 0.01 gram (1,000 to 100,000 units).

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ŒSTRADIOLIS MONOBENZOAS, œstradiol monobenzoate, dihydroxyœstrin monobenzoate, $C_{25}H_{28}O_3$, α-3:17-dihydroxy-$\triangle^{1:3:5}$-œstratriene-3-benzoate. Dose, subcutaneously or intramuscularly, 0.0001 to 0.005 gram (1,000 to 50,000 units).

STILBŒSTROL, diethylstilbœstrol, 4:4″-dihydroxy-α:β-diethylstilbene. Dose, 0.0005 to 0.002 gram.

TABELLÆ STILBŒSTROLIS, tablets of stilbœstrol. Dose, 0.0005 to 0.002 gram.

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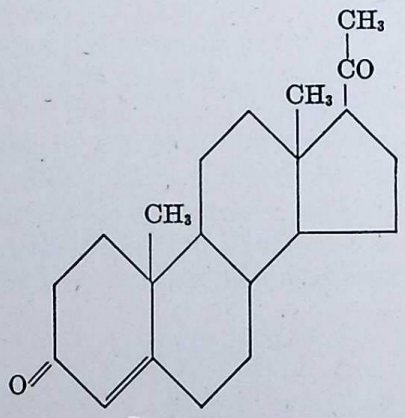
Nomenclature, Ibid., **107**, 1221, 1936.
ROBISON: Recent Advances in Sex and Reproductive Physiology, Philadelphia, The Blakiston Company, 1940.
SONDERN AND SEALEY: Endocrinology, **27**, 670, 1940. (Assay.)

Progesterone—the Hormone of the Corpus Luteum.—As already indicated the corpus luteum which appears following ovulation secretes a hormone with important physiological actions on the uterus, its adnexæ and the mammary glands. The most active principle which has been isolated from corpora lutea is progesterone, a compound having the formula:



Progesterone
$C_{22}H_{31}O_2$

Progesterone is prepared synthetically from stigmasterol. Amorphous concentrates derived from corpora luteal tissue, which possess progestational activity and are designated as "progestin," are also available for clinical use. These preparations dissolved in oil are all administered parenterally.

A third preparation—**ethinyl testosterone** or **anhydro-oxyprogesterone**—possesses progestational activity and is marketed for oral administration.

Therapeutic Use.—Experimental experience would seem to indicate that progesterone or other preparations manifesting progestational activity might be useful in cases of sterility or of habitual abortion which are due to lack of this hormone. It might act either by quieting the contractions of the uterus or by acting on the mucosa of the uterus so

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as to make it favorable for nidation. It has also been tried in menorrhagia and in metrorrhagia, inasmuch as in certain forms of uterine hemorrhage produced experimentally it has lessened the bleeding. Such use in the clinic would for the present be of an experimental character. It is claimed also to lessen the pain in threatened abortion and also in dysmenorrhea, and any such action would probably be due to its causing relaxation of the uterus.

Progesterone is also used in combination with estrogenic hormone in the treatment of amenorrhea.

PREPARATIONS

B. P.

PROGESTERONUM. Crystalline Δ^4 pregnene, 3:20 dione. $C_{21}H_{30}O_2$. Average dose, 5 mg. in oil, intramuscularly.

Non-official

ANHYDRO-HYDROXYPROGESTERONE. Synthetic Δ4-pregnene-17-ine-17 [α]-ol-3-one. $C_{21}H_{28}O_2$. Average dose, 10 mg., orally.

REFERENCES

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3. Male Sex Hormones

For almost a hundred years it has been known that the testes exert an action upon the growth of cockerel combs by a humoral mechanism, but it is only in comparatively recent years that the presence of a male hormone was positively demonstrated by McGee (1927), who showed that the lipid fraction of extracts of bull's testes will induce such comb growth. This work was speedily confirmed and extended to show that these extracts could also prevent or repair changes in the accessory reproductive organs of mammals which were the result of castration. These extracts were crude mixtures and were referred to under various names such as "bull testis extract," testicular hormone, male hormone, etc.

Shortly after the demonstration of the hormonal activity of extracts of the testes, Funk and Harrow (1929) obtained extracts from the urine of males possessing very similar physiological effects. This product of the male urine was designated also as the "male hormone" and to distinguish it from the testicular product it was referred to as the "male hormone from urine."

Two years later Butenandt (1931) obtained a compound from human male urine in crystalline form and showed that it acted upon the capon comb and upon the male accessory reproductive organs. This crystalline substance was named "androsterone" and its formula shown to be $C_{19}H_{30}O_2$. Soon afterward it was prepared synthetically from cholesterol. Butenandt and his co-workers also isolated a second crystalline hormone from human male urine which was found to be dehydroandrosterone

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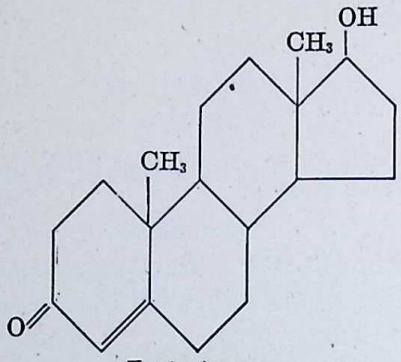
($C_{19}H_{28}O_2$). This, too, exerted similar effects to androsterone itself, but it required considerably larger doses to produce like effects.

In 1935 a crystalline body was prepared from the testicular tissue and was shown to be very much more active on mammalian tissues than was androsterone. This crystalline body which possessed the formula $C_{19}H_{28}O_2$ was named "Testosterone." Shortly afterward it too was prepared synthetically by Ruzicka, and shown to have the following structural formula:



Testosterone
$C_{19}H_{28}O_2$

Testosterone is inactive when administered orally. Its **methyl derivative**, however, is active when given by this route.

The **action** of male hormones is essentially one of a replacement nature, restoring the normal structure and function of the accessory genital organs in eunuchs and in castrated animals. The male hormones do not stimulate the hormonal activity of the testes, even though they aid to a certain extent in the maintenance of spermatogenesis. In large doses they may be injurious to the interstitial tissue, since they act upon the anterior lobe of the pituitary, suppressing the gonadotropic hormone in the same manner as do the estrogenic substances.

Therapeutic Uses.—The androgens (testosterone propionate and methyl testosterone) are used in eunuchoidism to stimulate the growth of the penis, pubic and facial hair and the development of a masculine voice. They are also used occasionally to overcome the nervous symptoms sometimes seen in elderly men, which have been considered as analogous to the menopausal syndrome observed in women. However, the value of androgens in the latter condition is still not established.

The androgens are also widely used in gynecology for such diverse conditions as menstrual disturbances, painful breast engorgement, functional dysmenorrhea, in the menopausal syndrome, etc. In administering androgens to women it is important that the dose used be less than 150 to 300 mg. of testosterone or its equivalent per month. Otherwise, there is danger of inducing undesirable masculinizing effects.

The androgens are administered by intramuscular injection of testosterone propionate in oil, orally in the form of methyl testosterone, by inunction of testosterone propionate into the skin, or by the implantation of pellets of testosterone where continued action over a long period is desirable, as in the treatment of eunuchoidism. The average dose of

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testosterone propionate is 25 mg. by injection. Methyl testosterone is administered in the form of 10 mg. tablets, orally. Pellets of testosterone weighing 75 mg. are used for subcutaneous implantation.

PREPARATIONS

Non-official

TESTOSTERONE PROPIONATE. Synthetic, $\triangle$4-androstene-(17α)-ol-(3)-one-(17)-propionate. $C_{22}H_{32}O_3$, Average dose, 25 mg. in oil, injected intramuscularly.

METHYL TESTOSTERONE. Synthetic, 17-methyl-$\triangle$4-androstene-17-α-ol-3-one. $C_{20}H_{30}O$. Average dose, 10 mg. orally.

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RUZICKA: Chem. Rev., **20**, 69, 1937.

I. HEMATICS

Anemia, which usually refers to a reduction in the amount of the hemoglobin or the number of red blood corpuscles in the blood, may be due to a variety of causes. Anemia resulting from a deficiency of iron has already been considered in an earlier section. Anemia may also result from blood loss, wasting diseases (*e. g.*, cancer, leucemia, etc.), specific deficiencies (avitaminosis, hypothyroidism, etc.), blood destruction (hemolytic anemia, sickle cell anemia, etc.), or a decreased blood production. Among the last-named is included pernicious anemia (Addisonian Anemia) which responds to specific therapy with liver and stomach preparations, to be discussed next. There will then be considered other drugs which affect the blood and hence may be included under the general heading of hematics.

1. Liver and Liver Preparations

Minot and Murphy in 1926 made the important therapeutic discovery of the remarkable effects which follow the administration of liver to cases of primary (pernicious) anemia. A direct outgrowth of the careful work carried on by Whipple and his associates upon the effects of various preparations of iron and of articles of food upon secondary anemias, these workers were able to present the records of 45 cases of primary anemia which had responded favorably to a diet containing a considerable amount of liver. The results obtained by Minot and Murphy were soon confirmed and indeed the action of liver in primary anemia is now so well established that in a suspected case of the disease if an adequate amount of liver is given and none of the

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expected changes in the blood picture follow it is probable that the diagnosis of primary anemia is incorrect.

Following the administration of a sufficient dose of liver, which as experience has shown is about half a pound a day, there will be definite changes in the blood picture, the extent of such changes being dependent upon the degree of anemia present when the diet of liver is initiated. Usually about the fourth day the reticulocytes, which normally exist in human blood to the extent of about 1 per cent, begin to increase in number. This increase continues for four or five days, usually reaching its maximum between the seventh and the ninth day after which time the curve of increase begins to decline, reaching the normal again about the twenty-first day. The extent of increase in the number of reticulated red cells will depend upon the number of red blood cells in the patient's blood when the treatment is begun. The lower the red cell count the greater is the increase in the number of reticulocytes which will be present in the blood. For example, a patient with a red cell count of 600,000 would be expected to have an increase in reticulocytes to about 50 per cent of his total number of red cells after taking an adequate amount of liver or liver extract by mouth. With an initial count of 1,000,000 a reticulocyte count of 41 per cent would be expected, while with a count of 2,000,000 there would be about 18 per cent reticulocytes and with 3,000,000 red cells about 5 per cent reticulocytes. Following this outpouring of young red cells the total red cell count begins to rise. This increase is a gradual one so that in the course of a few weeks a normal count of 4,500,000 or 5,000,000 may be reached. It is interesting that with adequate amounts of liver the red blood cell count in patients will reach normal in eight weeks no matter what was the initial red cell count. A patient with a count of 3,000,000 or 2,000,000 reaches the 5,000,000 level no earlier than one with a count of 1,000,000 or even 500,000. The lines of increase all converge to meet at the common point at the eighth week. At the same time as the red cells increase in number certain abnormalities of the blood disappear. The cells become more normal in size, shape and color. The abnormally large cells which are distorted in shape and the red cells which are nucleated disappear, and cells having a normal size and shape gradually replace them.

In addition to the changes in the blood there are signs of clinical improvement which appear soon after the liver diet has been instituted. After two or three days the patient begins to feel better, his appetite improves and he feels stronger. His color improves. The pads of the fingers and the palms of the hands, the cheeks and the tip of the nose all begin to show a pink flush even before there is any marked change in the blood count. The feeling of nausea disappears and the intestinal condition is better. The condition of the tongue usually improves although in certain cases not to the same extent that there is improvement in the general health. A similar statement applies to the neurological changes which are sometimes present in this disease. Definite degenerative changes which the nervous system may have undergone are usually not appreciably altered by the liver diet. In this connection the maintenance of a normal blood condition seems to be of great

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importance and frequently symptoms resulting from changes in the nervous system, such as tingling or numbness, may be benefited or entirely disappear with the improvement in the condition of the blood. The condition of achlorhydria which is practically always present in the primary anemia is apparently not benefited by a liver diet.

So far as is known in such cases of primary anemia liver in some form (or one of the other specific products used in this disease) will have to be continued throughout the patient's life, the dose necessary for maintenance of good health differing with different individuals but averaging about one-half pound of liver five times a week or an equivalent amount of one of the extracts which have been introduced to replace the liver itself.

The existence of an infectious process in a patient, such as a common cold, tonsillitis, bronchitis, and particularly infections of the urinary tract, may interfere with the effects of liver and delay the reticulocyte increase but with recovery from the infection the beneficial effects from the diet will become manifest again. Also during a therapeutic remission in the disease when the patient is on a uniform maintenance diet, the occurrence of some acute infection with fever will usually be followed by a lowering of the blood count unless the dose of liver is augmented to compensate. Inadequate responses are also noted in older patients, those with arteriosclerosis, and in those in whom absorption or storage is deficient.

Preparations.—In spite of the brilliant results which follow the treatment of cases of primary anemia with a diet containing liver, the use of such a diet has certain disadvantages. One very practical difficulty with it is that patients get very tired of taking liver every day and again others are unable to tolerate the necessary quantity on account of gastro-intestinal symptoms. These objections to the liver have been overcome in various ways, especially by the preparation of partially purified preparations and extracts which can be taken by mouth or in other cases can be injected intramuscularly or intravenously. Each of these modes of administration has advantages which are apparent. For the average patient the use of an extract by mouth is doubtless the most simple, provided the patient does not get careless and neglect his treatment. By injection into the muscles, the dose of liver which it is necessary to administer in order to insure satisfactory results is much less than when extracts are given by mouth. For instance, the daily intramuscular injection of material prepared from 10 to 15 grams of liver is approximately equivalent in efficiency to an extract prepared from 300 grams, when given in daily doses by mouth. Still more highly purified extracts of liver have been prepared containing as much as 15 units per cc., but the objection to such concentrated solutions is that in their preparation a considerable loss of potency occurs, making the use of a larger amount of liver necessary and other factors than the anti-anemic principle may be lost during the process of purification. Experience in the individual case only will show the most favorable time interval between injections and also the dose necessary in each case to

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maintain a normal blood picture and the other signs of remission of the disease.

The advantages of giving the material parenterally are manifest. There is not only economy of liver and relief from what becomes a tiresome article of food, but also avoidance of carelessness on the part of the patient due to neglect to take the diet. Intravenous administration is rarely necessary or advisable and hence the intramuscular route is used almost exclusively when parenteral administration is desirable. The parenteral method of administering the liver is more efficient than the oral method in bringing about improvement in symptoms due to neurological changes which may have appeared during the course of the disease. In patients manifesting damage to the central nervous system as well as in case of sprue, the use of crude liver is preferable to the extracts since the former contains nutritional factors in addition to the anti-anemic principle.

The available **preparations** of liver include: a dry extract and solution for use by mouth, and a purified solution for intramuscular injection. All of these preparations have to be assayed for potency on patients suffering from pernicious anemia according to methods approved by the Anti-anemia Preparations Advisory Board of the United States Pharmacopeia and have to meet its standards. Liver extracts are prepared from ox or sheep liver by means of acid alcohol, in which the active principle is soluble. After concentration and purification it is reduced to a light brown powder with a meaty odor and taste. It is freely soluble in water. Extracts for injection are subjected to further purification.

Combinations of liver and stomach preparations are also available and will be discussed in the next section (page 579). In view of the fact that liver is an excellent source of the vitamin B complex various combinations of liver extract and vitamins are also available. These will be discussed under Vitamins (page 583).

Assay.—At present no satisfactory method of testing is available other than in the clinic, where it is administered to patients who have primary anemia and who are in a state of relapse and to whom no liver or other preparation having a specific action in the disease has been given recently. In such a case a preparation, if it is potent, will bring about the typical increase in reticulocytes and in numbers of red blood cells.

The potency of anti-anemic preparations is expressed in terms of "U. S. P. units" defined as the minimal amount which given daily in an uncomplicated case of pernicious anemia will produce a satisfactory reticulocyte response.

Dosage.—The dosage required in treating macrocytic anemias with liver preparations is variable. Larger doses are necessary in elderly patients, in the arteriosclerotic, in the presence of infections, in patients in whom absorption from the gastro-intestinal tract is defective, as in severe diarrhea, and in those suffering from marked neurological involvement.

In the severely anemic patient, 10 units are injected intramuscularly

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in one dose or in divided doses during the first six hours. Thereafter, 5 units are injected daily until the maximum reticulocyte response is obtained usually in five to seven days. The dose is then decreased to 10 units weekly. With an initial red blood cell count of 3,000,000 or more, 30 units may be injected during the first two weeks, at the end of which time a definite increase in the red blood cell count and volume of the packed red cells should be evident.

The maintenance dose is one unit per day. This may be administered by the intramuscular injection of 15 units every two weeks.

The **mode of action** by which preparations of liver bring about a remission of the symptoms of primary anemia is not known. This disease is believed to be the result of a deficiency of a factor which normally acts upon the bone marrow and is essential for the proper maturation of the red blood cells. This essential factor is believed to be formed by the interaction of the so-called "intrinsic factor" of Castle which exists in the gastric juice with the "extrinsic factor" present particularly in meats. In Addisonian anemia it is the intrinsic factor which is lacking. This is probably an enzyme, and is destroyed by heating to 70° C. Under normal conditions the substance formed by the interaction of these two factors is probably stored in the liver and is called upon as needed to act upon the bone marrow. In the absence of this principle the bone marrow undergoes the megaloblastic hyperplasia which is characteristic of this disease. It has been shown that when the liver diet is administered and the condition of the blood is improving, the megaloblasts in the marrow decrease and the appearance of the marrow approaches normal. The rapid increase in the very young red cells following the administration of liver in some form is very suggestive that the diet furnishes the necessary stimulant for the maturation of the red blood cells.

The **chemical nature** of the material in liver which is active in pernicious anemia is unknown. It is non-protein, freely soluble in water and in slightly acid alcohol. The purest preparations contain only carbon, hydrogen, oxygen and nitrogen but no phosphorus or sulfur. Angier and his collaborators have recently isolated and synthesized a factor from liver extracts which manifests hemopoietic action. The relation of this compound to the active principle effective in pernicious anemia remains to be determined. They may be identical. A further discussion of the hemopoietic action of the vitamins is given later (page 602).

Therapeutic Uses.—Liver and its derivatives are of use only in the anemias in which a defective formation, absorption or storage of the active material results in failure of proper maturation of red blood cells. These are the macrocytic anemias. Included in this group of anemias, in addition to pernicious anemia, is the anemia due to tropical sprue where there may be lack of the extrinsic factor in the diet and impaired absorption in the intestine. Liver therapy is very effective in this condition. In pellagra there is apparently a similar disturbance of the factors concerned in proper blood maturation and here, too, liver therapy has been found useful in addition to nicotinic acid which, incidentally, is present in high concentration in crude liver extracts.

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In cirrhosis of the liver, liver therapy has also been found to be effective in overcoming the macrocytic anemia often associated with this disease.

Preparations

U. S. P.

Extractum Hepatis, dry liver extract, a dry brownish, somewhat hydroscopic powder containing the soluble thermostable fraction of mammalian livers. Dose, one U. S. P. unit daily.

Liquor Hepatis, solution of liver, liquid extract of liver, a brownish liquid. Dose, one U. S. P. unit daily, orally.

Injectio Hepatis, liquor hepatis purificatus, liver injections, a sterile solution in water. Dose, one U. S. P. unit daily by intramuscular injection.

B. P.

Extractum Hepatis Liquidum, liquid extract of liver. Dose, 30 mil.

Extractum Hepatis Siccum, dry extract of liver. Dose, the quantity equivalent to 225 grams, or about one-half pound of fresh liver.

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2. Stomach Preparations

Following the demonstration of the effect of feeding liver, kidney and other organs to animals in which a secondary anemia had been produced by bleeding, and the spectacular results obtained in pernicious anemia by the use of a liver diet, it was shown by Castle that something was secreted by a normal stomach which would act upon meat, producing in the process of digestion some substance which was absorbed and acted upon the bone marrow, bringing about maturation of the red blood cells. This substance is under normal conditions stored in the liver and kidney, imparting to these organs, as well as to others, their specific effects upon the bone marrow.

Following the discovery of this action of normal gastric juice in the production of the anti-anemic substance, equally good results were obtained by feeding to patients with primary anemia the gastric wall of animals after it had been chopped fine, dried and defatted by the use of petroleum ether. The administration of such material is followed by the same improvement in the blood and in clinical symptoms as results from the giving of liver preparations. A daily dose of about 40 grams of this desiccated, defatted material, corresponds to one U. S. P. unit and is sufficient to bring about a remission in pernicious anemia.

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The mode of action of the gastric material has not been explained. It appears probably that the intrinsic factor present in the mucosal cells of the stomach reacts with the proteins present in the stomach wall during *postmortem* autolysis, producing the anti-anemia factor which is found in the liver. As the material from the stomach is thermolabile and cannot be extracted by the same physicochemical means used in extracting the thermostabile material from liver, it must undergo further changes during absorption.

The changes in the blood and in the general condition of the patient are much the same after the taking of gastric material as after taking liver extract. On the third or fourth day the reticulocytes increase in number, reach their maximum and decline to their normal in about two weeks. The red blood cells gradually increase in number as after liver, and the appetite of the patient improves and he feels stronger.

The anti-anemic principle is also present in yeast, kidney and other sources but these are not used to an appreciable extent as therapeutic measures in treating macrocytic anemias.

In addition to dried stomach tissue, the combination of liver and stomach tissue is also used in the treatment of pernicious and other forms of macrocytic anemia. As shown by Walden and Clowes, the digestion of fresh stomach tissue with liver tissue or purified liver extract (Cohn's fraction G) results in a preparation which has a potency three to four times that of the raw liver from which it is derived. This concentrate (Extralin) is administered in doses of 2 grams three times a day which supplies the equivalent of 1 U. S. P. oral unit of liver.

Therapeutic Use.—Powdered stomach and liver-stomach concentrates are used in the treatment of pernicious anemia. Only preparations for oral administration are available. They are given in doses corresponding to 1 U. S. P. unit daily but the amount necessary for maintenance varies with different individuals and must be determined by repeated examinations of the blood.

PREPARATIONS

U. S. P.

STOMACHUS PULVERATUS, powdered stomach, the dried and powdered defatted wall of the stomach of the hog. Dose, one U. S. P. unit daily.

REFERENCES

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3. Pentnucleotide

The sodium salts of the pentose nucleotides derived from ribonucleic acid of yeast are used in conditions accompanied by leukopenia or neutropenia, such as agranulocytosis in which there is a decrease in the number of circulating polymorphonuclear leucocytes. Agranulocytosis is observed most commonly as a toxic reaction following the

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administration of certain drugs particularly aminopyrine, the sulfonamide derivatives, gold salts, the arsenicals, etc. Pentnucleotide exerts its action presumably by stimulating the bone marrow. It is ineffective in conditions such as aleukemic leukemia or aplastic anemia nor is it always effective in other conditions.

Pentnucleotide is administered in doses of 10 cc. by injection into the gluteal muscles, four times daily. A response as noted by the appearance of myelocytes and young polymorphonuclears in the blood smear may be evident in thirty-six to forty-eight hours, but often will not appear for five or more days.

Untoward but not severe reactions characterized by dyspnea, precordial distress, bradycardia, sweating, vomiting and occasionally chills and fever follow the use of pentnucleotide.

Recently the use of various fractions of vitamin B complex have also been advocated for the treatment of agranulocytosis. Transfusions of fresh blood are also used but it is difficult to evaluate the efficacy of all of these drugs and procedures since the patients often recover spontaneously when the drugs responsible for the condition are withdrawn.

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4. Anticoagulants

Heparin.—Extracts from certain tissues have the property of preventing the coagulation of shed blood. An extract of buccal glands of the leech designated as **hirudin** was long used for this purpose until displaced by heparin, first prepared from mammalian liver and lung tissue by Howell and his co-workers. Heparin has been isolated in the form of a crystalline barium salt. On hydrolysis it yields *d*-glucosamine in large amounts together with uronic acid and sulfate. Heparin is therefore believed to be a mucoitin polysulfuric acid.

Heparin by its strongly acidic nature, is believed to form a complex with a factor present in serum albumin and thus acts as an anticoagulant by inactivating thrombin. Heparin and a co-factor present in blood plasma also inhibits the conversion of prothrombin to thrombin and prevents the agglutination of platelets.

Purified preparations of heparin suitable for intravenous injection into man are commercially available. The unit of activity is defined as the activity present in 0.01 mg. of the crystalline barium salt. One mg. of this material will prevent the clotting of 500 cc. of cold cat's blood for twenty-four hours.

Heparin is used to prevent the coagulation of blood *in vitro* in cases where it is undesirable to use such anticoagulants as citrate, oxalate or fluoride. It is also administered intravenously in patients in whom it is desired to retard the coagulation of the blood. It may also be administered subcutaneously in a menstruum containing gelatin and dextrose

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(Loewe and Rosenblatt). The latter procedure permits the prolonged absorption of the drug at a uniform rate and lessens the necessity of frequent injections with abrupt decrease in the coagulability of the blood to dangerous levels.

The use of heparin in the intact organism requires care, for when the coagulability of the blood is much reduced there is always the danger of spontaneous hemorrhage into the brain. It has been replaced clinically to a large extent by dicumarol.

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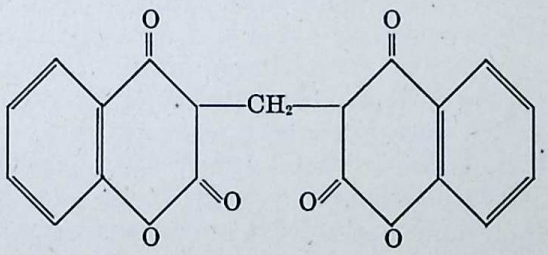
Dicumarol.—The existence of a hemorrhagic diathesis in cattle eating improperly cured clover was found to be due to the presence of 3,3′-methylenebis-(2,4 diketochromane). This substance was isolated and synthesized by Link and has been used clinically under the trade-



Dicumarol

name, *Dicumarol,* for the prophylaxis and treatment of intravascular clotting. Dicumarol prolongs the prothrombin time by interfering apparently with the function of vitamin K, which it resembles in structure (*cf.* page 610). The effects of dicumarol may be counteracted by the administration of large amounts of vitamin K. Unlike heparin it is without effect when added to shed blood.

Dicumarol is used as an adjunct to or as a replacement for heparin over which it has the advantages of cheapness, of being effective orally and of having a more prolonged action. Its disadvantage compared to heparin is the slow onset of its action as a result of which heparin must be used when a prompt effect is desired. There is usually a lag of twenty four to forty-eight hours in attaining the full effects of dicumarol.

The clinical use of dicumarol must be controlled by daily prothrombin determinations, since the individual response to the drug varies greatly. It is administered orally in an initial dose of 5 mg. per kilo of body weight with the subsequent dosage determined by daily prothrombin time levels. If the prothrombin activity is reduced to less than 25 per cent no further dicumarol is administered. Overdosage with dicumarol

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necessitates transfusion of fresh blood and the intravenous injection of large doses (40 mg.) of menadione (vitamin K).

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REICH, YAHR AND EGGERS: Surgery, **18**, 238, 1945.
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5. Coagulants

Fibrin.—The clotting process may be represented as occurring through two reactions:

$$\text{Prothrombin} + Ca^{++} + \text{Thromboplastin} \longrightarrow \text{Thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin}$$

A deficiency of vitamin K as we shall see (page 610) results in a lack of prothrombin while a deficiency of thromboplastin is the cause of impairment of the clotting process in certain congenital disorders. In the presence of fibrinogen in the blood, the addition of preformed thrombin will result in the formation of fibrin. Thrombin is obtained during the processing of human blood for the preparation of plasma and, as a by-product, has been introduced into surgery for use in arresting hemorrhage. It is used in the form of *fibrin foam*, a sponge-like material which may be left in position after closing the wound since it is readily absorbed. Fibrin, and fibrin foam have been especially useful in neurosurgery. Absorbable oxidized cellulose is also available for use as a hemostatic in surgery.

Fibrin and fibrin foam have largely replaced the **fibrin ferments** and **thromboplastic substances** previously used locally to stop hemorrhage. The fibrin ferments and thromboplastin are prepared by extraction of brain tissue. Their action depends on their capacity to induce the formation of thrombin from prothrombin in the presence of calcium ion. They are used as hemostatics for local application to bleeding surfaces. Thromboplastin is also available commercially for use in the determination of the prothrombin time of the blood.

The use of ferric salts as stypics to control local hemorrhage of vasoconstrictors and of vitamin K in prothrombin deficiency are described elsewhere under these headings (see pages 113 and 611, respectively).

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J. VITAMINS, OR ACCESSORY FOOD SUBSTANCES

Vitamins are substances which must be supplied in small quantities to maintain normal health; if one of them is inadequate, the deficiency leads to the development of disease and death or permanent impairment of health; but if the lacking constituent of the dietary is given before irretrievable damage has occurred in the tissues, complete recovery generally follows. The amount of these substances necessary to maintain health is so small that they cannot be regarded as sources of energy like the ordinary foods. The vitamins resemble drugs in certain respects and are analogous in their action to the hormones which have been aptly termed "endogenous vitamins."

The fact that small quantities of apparently indifferent substances are necessary to health was first appreciated a century and a half ago, when it was noted that scurvy could be cured by fresh vegetables or by the juice of lemons and other similar fruits. At the beginning of the present century it was discovered that beriberi, a disease which is seen chiefly in rice-eating countries and which became very prevalent when polished rice was introduced, could be remedied by treating the patients with less completely prepared rice or with the germ which had been removed in the process of polishing. But the subject received the attention it deserved only when it could be accurately examined by means of animal experiments. At the same time it became clear that in modern populations and with the present methods of preserving and storing foods there is a possibility that these and other "deficiency diseases" may become prevalent; many people consuming food adequate as far as the provision of energy is concerned live on the borderline below which the vitamins are deficient and ill health results. It is also true that persons on a badly balanced diet or patients on a highly restricted regimen do at times exhibit signs of vitamin deficiency.

Recognition of the fact that in the preservation of foods under commercial conditions certain of the vitamins are likely to be destroyed in whole or in part has led some of the manufacturing establishments to adopt procedures adapted to lessen exposure of the food to the action of oxygen when it is being canned and the cans themselves before being sealed have the oxygen exhausted or replaced by nitrogen. For man, like the other animals, cannot manufacture those essential substances, but derives his supply from vegetables either directly or through the flesh of animals which have absorbed them in their food. Nursing infants draw their supply of vitamins from the mother's milk, and a deficiency in her food often gives rise to symptoms in the child; these disappear at once on supplementing the mother's diet where necessary.

A number of vitamins are recognized at present and it is not unlikely that there may be others or perhaps that some of those now recognized may prove to contain two or more different principles. Many of the vitamins have been isolated in pure chemical form and their chemical composition established and some have been synthesized. The synthetically prepared vitamins are added to certain food products (par-

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ticularly bread) in order to replace the naturally occurring vitamins removed or destroyed in the process of preparation. Several of the vitamins have been shown to be components of certain enzyme systems which accounts for their vital rôle in the body.

Ordinarily a properly selected diet will afford an adequate supply of the requisite vitamins. Under conditions of a restricted diet a relative shortage of some of the vitamins may, however, arise. The chief indications for the use of vitamin preparations are as prophylactics when an inadequate intake may be anticipated (*e. g.* vitamin D in infants) or when definite avitaminosis exists. The promiscuous use of vitamin preparations where no such indications exist is to be deprecated.

Preparations

U. S. P.

The mixtures of various vitamins which have been accorded pharmacopeial recognition are cited here. The preparations of the single vitamins are given under their respective headings.

Capsulæ Hexavitaminarum, hexavitamin capsules, contain 2500 U. S. P. units of vitamin A, 200 U. S. P. units of vitamin D, 37 mg. of ascorbic acid, 1 mg. of thiamine hydrochloride, 1.5 mg. of riboflavin, and 10 mg. of nicotinamide. Dose, according to the needs of the patient.

Tabellæ Hexavitaminarum, hexavitamin tablets. Potency and dosage as in preceding.

References

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Rosenberg: Chemistry and Physiology of the Vitamins, New York, Inter-Science Press, 1942.
Sherman: Chemistry of Food and Nutrition, Essentials of Nutrition, The Macmillan Company, New York, 1946.

Vitamin A

This vitamin has been known as the anti-ophthalmic vitamin due to the fact that its absence from the food will result in a condition in which there is a characteristic eye disturbance which is known as xerophthalmia. However, the symptoms in this disorder are much more widespread, not being limited by any means to the eye, so that this vitamin is not infrequently referred to also as the "growth promoting" factor A. It has also been called the "anti-infective" vitamin but there is no evidence to justify such a name. Any such effect is, in the light of present-day knowledge, only indirect in that the vitamin assists in preserving the health and vigor of the body.

Chemistry.—Vitamin A, being soluble in fats and oils, was in the earlier work upon these substances confounded with other fat-soluble principles or rather these vitamins, so far as they were known, were all grouped together. Now, however, three distinct fat-soluble vitamins have been recognized, and the two which have been differentiated from A are now classified separately as vitamin D, or the antirachitic principle; and E, or the antisterility factor.

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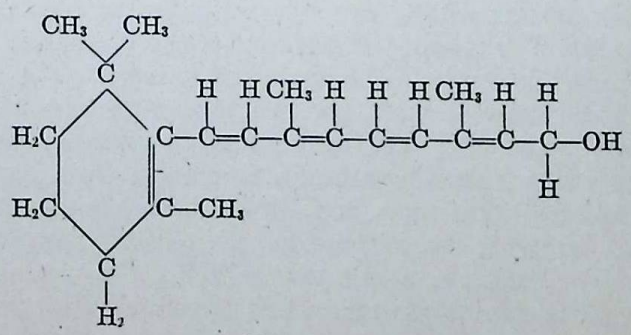
The presence of a large amount of a yellow pigment in plants which contain an abundance of vitamin A led to a further study of such carotenoid pigments and of their relation to the activity of this vitamin. Many of these yellow pigments are designated by special names such as zeaxanthin, from yellow corn; capxanthin, from the red peppers; flavoxanthin, from the buttercup; and toxaxanthin, from dandelions. Many of the green foods which contain the vitamin are rich in this yellow pigment, the presence of which is concealed by the green color. In fact, there seems to be a relationship between the green coloration of various food products and their vitamin A content. The green leaves of lettuce are richer in this vitamin than are the white leaves of head lettuce, and green asparagus tips are more potent than the white. However, cod-liver oil, which is rich in this vitamin, contains none of this pigment.

The pigment, which is known as **carotene**, has been isolated in pure form and has the formula $C_{40}H_{56}$. The molecule of carotene is capable of being split in half, with the formation of an alcoholic group at the end of each split product forming the vitamin A. Carotene differs from the vitamin in certain important respects. For instance, the latter is almost colorless, and in addition it has spectrographic properties differing from those possessed by carotene. Carotene itself is exceedingly active, a daily dose of 0.003 mg. being sufficient to prevent the symptoms of avitaminosis in the rat. It is a hydrocarbon and occurs in three forms, which have been designated as alpha, beta, and gamma carotene. The beta carotene is twice as active as either the alpha or gamma, but in nature they usually appear as a mixture of the three. The vitamin A activity of yellow maize is not due to carotene but rather to a closely related pigment, cryptoxanthin. The changes in the body which are ascribed to vitamin A activity are believed, therefore, to be due to five substances—vitamin A itself; alpha, beta, and gamma carotene; and cryptoxanthin. The last four are precursors of the vitamin and are found in the plant kingdom. In the animal body they are changed into a compound with the formula $C_{20}H_{29}OH$, which is known as vitamin A. The transformation from precursor to vitamin occurs in the liver through the action of an enzyme, **carotenase**, and storage of the substance is also largely in that organ.



Vitamin A

The structure of vitamin A was elucidated by Karrer. It has been isolated in crystalline form (Holmes) from fish liver oil and synthesized (Batty, *et al.*).

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Two isomeric forms of vitamin A have been isolated and they are designated as vitamin A_1 and A_2, respectively. The common form which is present in the livers of salt-water fish has the formula shown above and is known as vitamin A_1. Vitamin A_2 is found in fresh-water fish and contains two less hydrogen atoms and an extra double bond. It differs from vitamin A_1 in spectrum and color tests.

Occurrence.—Vitamin A is found primarily in plants, the green leaves being especially rich, but it is found also in the actively growing parts of the plants such as the young shoots, while the storage parts of the plant such as fleshy roots and tubers have much smaller amounts. Natural yellow color is a rough guide for the selection of vitamin A in animal products as it indicates the consumption of the vitamin precursors by the animals. However, some vitamin-rich products are poor in pigment, as for example halibut- and burbot-liver oils. Yellow maize is richer than is white maize and sweet potatoes contain more than white potatoes. Animals receive their supply of this factor from plants and store it up in the various tissues and organs, especially in the liver, kidneys, and lungs. The liver, for instance, has been shown to contain from 200 to 400 times as much as muscle tissue, and the lungs and kidney are 40 times as rich as muscle. Inasmuch as this vitamin is so important for growth it is interesting to find it in large quantities in milk and in the yolk of eggs. In fact, milk, eggs and green vegetables are the chief sources of this vitamin for man. Cod-liver oil has long held a position of importance in medicine because it contains large amounts of this vitamin in addition to the antirachitic factor (vitamin D). The livers of other fish than the cod contain much larger quantities of this vitamin than does the liver of that species. For example, the liver of the halibut may contain 100 times as much; in fact 1 per cent by weight of halibut-liver oil may be vitamin A. The cod, like other fish, gets its supply of vitamin indirectly from the algæ upon which the smaller fish and lower forms of marine life feed, and these small fish serving as food for the cod furnish it with the vitamin, which in turn is stored in the fat of the liver.

On account of its solubility in fats, vitamin A is stored in the animal body in larger amounts than are some of the other vitamins, so that no symptoms of deprivation are seen until this store has become exhausted. Young adult rats apparently can store sufficient to keep them alive for about six months. Probably 95 per cent of the vitamin is stored in the liver, with small amounts in the lungs and kidneys. The accumulation in the liver is lowest at birth and tends to increase with age and is dependent upon the diet. On this account the vitamin content of milk is very important. As the vitamin formation from carotene is not always complete, milk, eggs, and other foods contain a mixture of vitamin and carotene, the proportions of each varying often according to species. For example, about two thirds of the vitamin activity of Guernsey milk is due to carotene while Ayrshire milk owes about one-third of its activity to carotene, and in Jersey milk there are about equal quantities of vitamin and provitamin.

The vitamin A **preparations** used in medicine consist of carotene

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(Pro-vitamin A) preparations, fish liver oils derived from various species of Gaddus, Burbot and Percomorph fishes and from shark livers. The liver preparations are also rich in vitamin D.

Absorption and Excretion.—Vitamin A is absorbed well, reaching its maximum in from three to five hours after administration. Carotene absorption is more variable and is slower, reaching its maximum in from seven to eight hours. Carotene dissolved in oils or given with a fat diet is utilized well but when given with a low fat diet its absorption is less satisfactory. It should not be given with liquid petrolatum as it is soluble in this vehicle and therefore will not be absorbed. Excess of vitamin is stored as stated and the remainder probably destroyed as very little is found in the excretions.

Clinically, the earliest sign of chronic hypovitaminosis A is seen in a change in the skin. There appears a dryness of the skin, with a papular eruption **(follicular keratosis)** which affects particularly the extremities, shoulder, chest, and buttocks. Comedones appear in abundance. The resistance of the skin is lowered which predisposes to infection. It was the occurrence of these local infections, not only in the skin but also in the eye and elsewhere in the body, which gave rise to the idea that vitamin A was an anti-infective vitamin. The essential pathological changes in the skin are atrophy of the sweat and sebaceous glands and hyperkeratinization of the epithelium.

Also one of the early manifestations of lack of vitamin A, and usually following the skin changes as seen in adults, is night blindness **(nyctalopia)**, a condition where there is more or less difficulty in adapting vision where there is faint illumination. This disturbance of vision is apparently connected with failure of the visual purple of the retinal rod cells to regenerate after its exhaustion by exposure to bright light. Normally the vitamin brought to the retina unites with protein to form the visual purple. In the avitaminotic state the vitamin component is lacking, hence regeneration of the visual purple cannot take place. **Xerosis** or dryness of the conjunctiva is considered to be the second stage of eye disturbance, and this is succeeded closely by xerosis of the cornea and inactivity of the para-ocular glands with lessened secretion of tears.

In addition to the eye changes in the absence of this vitamin, animals cease to grow and become susceptible to the eye affections known as **xerophthalmia** and **keratomalacia.** The eye becomes sensitive to light; there is conjunctivitis with a purulent discharge. The lids are swollen and stick together and the cornea may become involved and blindness result. While the eye condition is one of the most striking signs of this deficiency disease it is by no means the only one. The resistance of the body is apparently lowered, and disease of the lungs is quite common, especially in the adult animal. Other signs of increased susceptibility to infection have been described, especially in the ears, in the sinuses, and in the glands at the base of the tongue. Doubtless some of these changes described are due to malnutrition and in others infection plays a part; for instance, in the production of the ophthalmia, infection doubtless is important, but that the lack of vitamin is the essential feature is shown by the rapid recovery when the same is supplied.

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The main pathological features of deficiency of vitamin A in man are therefore night blindness (nyctalopia), xerophthalmia, keratomalacia, and a definite kind of follicular keratosis of the skin.

Vitamin A then appears to act on the general nutrition of all the cells of the body. It is necessary for maintaining the structure of the epithelium of the skin, certain mucous membranes and glands, and for the normal function of the retina. The importance of an adequate supply of the vitamin for adults as well as for children should be generally recognized. It is best supplied in the form of milk, eggs, and green vegetables and, in case of need, cod-liver oil or halibut-liver oil, or other preparations of the vitamin.

Assay.—Vitamin A is assayed on rats maintained on a diet adequate except for a deficiency of the vitamin. It may also be determined chemically by the blue color which the vitamin gives with antimony trichloride, but this is not specific and hence suitable only for routine purposes of control. The International, U. S. P. and B. P. Standard is a pure specimen of beta-carotene, $C_{40}H_{56}$, which is dissolved in cocoanut oil. One international unit of vitamin A is defined as the activity equivalent to 0.6 γ. of the International Standard preparation.

Inasmuch as carotene is liable to deteriorate unless very carefully protected, a selected specimen of cod-liver oil is usually standardized against carotene, and this oil is then used in the evaluation of vitamin A products.

Therapeutic Uses.—The therapeutic value of vitamin A rests upon its action in those conditions resulting from its deficiency. Among these conditions are xerophthalmia, certain cases of night blindness, and follicular keratosis of the skin. It is also used in cases where there is reason to suspect an inadequate intake of the vitamin. As an aid to the development of bodily resistance to infection, it would be of value only when the stores of the vitamin in the body are exhausted or the intake inadequate. There is not sufficient evidence to show that its administration in excessive amounts has any value in the prevention of colds or of other infections. Also, as an aid to growth, it has not been shown to be of any greater value to the body than the other vitamins or the essential food constituents.

The daily requirement for vitamin A to allow for the maintenance of a moderate storage in the body is about 3,000 units for the normal adult and 6,000 to 8,000 units for the growing child. A supplement of some fish liver oil or other vitamin A preparation is recommended for children, particularly during infancy. During pregnancy 5,000 units or more should be available daily in foods rich in the vitamin supplemented if necessary by fish liver oil or other concentrates. During lactation 8,000 units a day are recommended.

In severe vitamin A deficiency the diet should be supplemented with 50,000 units of the vitamin. The clinical response is slow and treatment must be continued over a long period. In mild degrees of deficiency about 15,000 units daily are indicated.

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PREPARATIONS

U. S. P.

OLEUM MORRHUÆ, cod-liver oil, the U. S. P. requires that cod-liver oil shall contain at least 850 U. S. P. units of vitamin A as well as 85 U. S. P. units of vitamin D per gram. Dose, infants and adults, 8 cc.

OLEUM MORRHUÆ NON-DESTERARINATUM, non-destearinated cod-liver oil, the entire fixed oil. Potency as in preceding.

EMULSUM OLEI MORRHUÆ, emulsion of cod-liver oil. Dose, 15 cc.

OLEOVITAMINA A, natural vitamin A in oil, U. S. P. Vitamin A obtained from animal sources, either fish-liver oil alone, or fish-liver oil diluted with an edible vegetable oil, or a solution of vitamin A concentrate in fish-liver oil or in an edible vegetable oil. Natural vitamin A in oil contains in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not more than 1,000 U. S. P. units of vitamin D. Average daily dose: Prophylactic, infants and adults, 0.1 cc. ($1\frac{1}{2}$ minims).

OLEOVITAMINA A ET D, vitamins A and D in oil. Vitamins A and D obtained from animal sources, either fish-liver oil alone, or fish-liver oil diluted with an edible vegetable oil, or a solution of vitamin A and D concentrates in fish-liver oil or in an edible vegetable oil. The vitamin A must be obtained from natural sources; the D may be of natural origin or synthetic. Vitamins A and D in oil contain in each gram not less than 850 and not more than 1100 U. S. P. units of vitamin A, and not less than 85 and not more than 110 U. S. P. units of vitamin D. Average daily dose, 8 cc. (2 fluid drams).

OLEOVITAMINA A ET D CONCENTRATA, concentrated oleovitamin A and D. A concentrated form similar to the preceding preparation but containing in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not less than 10,000 and not more than 13,000 U. S. P. units of vitamin D. Average daily dose, prophylactic, infants and adults, 0.1 cc. ($1\frac{1}{2}$ minims).

CAPSULÆ OLEOVITAMINÆ A, oleovitamin A capsules. Capsules containing either 5,000 or 25,000 U. S. P. units of vitamin A per capsule. Average daily prophylactic dose, one capsule containing 5,000 U. S. P. vitamin A units.

CAPSULÆ OLEOVITAMINÆ A ET D CONCENTRATÆ, concentrated oleovitamin A and D capsules. Each capsule contains 5,000 U. S. P. units of vitamin A and 1,000 units of vitamin D. Dose, 1 capsule.

B. P.

OLEUM VITAMINATUM. Dose, prophylactic, 1 to 2 mil., equivalent to 1,000 to 2,000 international units of vitamin A and 100 to 200 international units of vitamin D; therapeutic, 3 to 6 mil.

OLEUM MORRHUÆ, cod-liver oil, contains not less than 600 units of vitamin A and 85 units of vitamin D per gram. Dose, prophylactic, 1 to 2 mil. three times daily; therapeutic, 3 to 6 mil. three times daily.

OLEUM HIPPOGLOSSI, halibut-liver oil. Dose, 0.06 to 0.3 mil. equivalent to 1500 to 7500 units of vitamin A.

EMULSIO OLEI VITAMINATI, emulsion of vitaminized oil. Dose, prophylactic, 2 to 4 mil. equivalent to 1,000 to 2,000 units of vitamin A, and 100 to 200 units of vitamin D.

EMULSIO OLEI MORRHUÆ, emulsion of cod-liver oil. Dose, prophylactic, 2 to 4 mil., equivalent to 1,000 to 2,000 units of vitamin A and 100 to 200 units of vitamin D.

LIQUOR VITAMINI A CONCENTRATUS concentrated solution of vitamin A. Dose, 0.06 to 0.3 mil., equivalent to 2,500 to 12,500 units.

LIQUOR VITAMINORUM A ET D CONCENTRATUS, concentrated solution of vitamins A and D. Dose, 0.06 to 0.3 mil. equivalent to 2,500 to 12,500 units of vitamin A, and 250 to 1,250 units of vitamin D.

EXTRACTUM MALTI CUM OLEO VITAMINATO, extract of malt with vitaminized oil. Dose, 4 to 16 mil. equivalent to 650 to 2,500 units of vitamin A, and 65 to 250 units of vitamin D.

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The Vitamin B Complex

Our present concept of vitamins was first developed from studies demonstrating the existence of a nutritional factor, the absence of which from the diet resulted in beriberi. Funk, in 1911, first prepared a concentrate from rice polishings which was active in the cure of beriberi, and because of its basic properties designated the active substances as a vitamine. The term was subsequently altered to vitamin so as to exclude the implication of a relation to the amines. As evidence was adduced to show the existence of several essential nutritional factors the term "water-soluble vitamin B" was introduced to differentiate this vitamin from the fat-soluble A. It is now known that the so-called vitamin B complex consists of a number of vitamins, some of which have been identified and synthesized.

The vitamin B complex is less stable than vitamin A, but some of its constituents withstand boiling for a short time and in acid or neutral solution are destroyed only slowly even when subjected to a high temperature; in the dry state they are even more stable. It is found in most forms of plant life but is concentrated in the seeds. Fruits, meat, particularly pork, milk, and eggs constitute good sources of the vitamin B complex. Milk is a valuable source, especially as it is usually not subjected to any treatment which would reduce its vitamin potency. Canned foods are believed to retain their potency well, as do also the foods which are preserved by freezing, although the vitamin is extracted quite easily in the case of frozen products so that expressed juices should be utilized.

The best natural sources for the vitamin B complex are rice polishings, yeast, and liver. Mixtures of synthetic preparations of constituents of the vitamin B complex, dried yeast, concentrates of brewer's yeast, liver extracts, and concentrates prepared from rice polishings are available for therapeutic use.

PREPARATIONS

U. S. P.

CAPSULÆ TRIASYNI B, triasyn B capsules, contain in each capsule not less than 1 mg. of thiamine hydrochloride, 1.5 mg. of riboflavin and 10 mg. of nicotinamide. Dose, according to needs of the patient.

TABELLÆ TRIASYNI B, triasyn B tablets, as in preceding.

CAPSULÆ TRIASYNI B CUM HEPATI, triasyn B with liver capsules. As in preceding with the addition of 0.5 gram of liver B-vitamins concentrate, together equivalent to not less than 1 mg. of thiamine hydrochloride, 1.6 mg. of riboflavin, 10.5 mg. of nicotinamide, and 6 mg. of choline.

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INJECTIO B-VITAMINARUM HEPATIS, liver B-vitamins injection, contains in each cc. the equivalent of not less than 0.08 mg. of riboflavin, 0.5 mg. of nicotinic acid, and 12 mg. of choline.

INJECTIO TRIASYNI B CUM HEPATI, triasyn B with liver injection, contains in each cc. the equivalent of not less than 3 mg. of thiamine hydrochloride, 0.5 mg. of riboflavin, 10 mg. of nicotinic acid, and 1 cc. of liver B-vitamins injection.

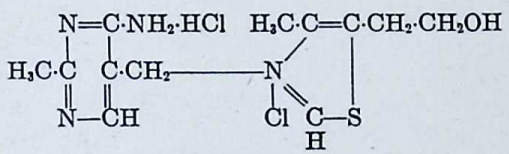
TABELLÆ SACHAROMYCITIS SICCI, dried yeast tablets. Dose in accordance with needs of the patient.

PERPOLITIONES ORYZÆ, rice polishings, the fine flaky pericarp and spermoderm fragments, the embryo, aleurone layer and outer adhering cells of the starchy endosperm.

EXTRACTUM PERPOLITIONUM ORYZÆ, extract of rice polishings. Dose, 8 cc.

Thiamine (Vitamin B_1)

Thiamine was the first recognized constituent of the vitamin B complex to be isolated in crystalline form. It is the antineuritic vitamin which prevents beriberi and polyneuritis.



Thiamine chloride hydrochloride

In 1936, Williams and Cline synthesized it and thus confirmed the structure which had been assigned on the basis of analysis of the products of degradation of the crystalline product. As seen in the accompanying formula, thiamine contains thiazole and pyrimidine rings and chemically is 2-methyl-5-(4-methyl-5-beta-hydroxyethylthiazolium chloride) methyl-6-aminopyrimidine hydrochloride.

Pathology.—Thiamine, being water-soluble, is stored in the tissues to a limited extent only, and a deficiency in the food elicits symptoms rapidly. In pigeons and the smaller animals a deficiency of this vitamin in the food may become noticeable in about two weeks, while in dogs symptoms may not appear for four weeks. Such of the vitamin as is stored is to be found in the liver which may contain ten times as much per gram as is found in voluntary muscles. The heart contains about the same amount in proportion to its weight as does the liver, while the kidneys and brain contain very little. If an excess of the vitamin is administered, it is quite rapidly excreted in the urine, and if diuresis is present, the amount of vitamin thus lost will be correspondingly increased. Ordinarily the vitamin is absorbed readily from the intestinal tract, but a serious disturbance of this organ, such as a severe diarrhea, may result in a considerable loss of the vitamin. From a pharmacological standpoint this vitamin has very little effect upon the organs of the body, such as the heart, gastro-intestinal tract, or on isolated tissues. Its action, therefore, is important up to the point of the needs of the body but not beyond.

A diet providing insufficient vitamin B_1 leads to malnutrition and retarded growth, but the most characteristic effect is the occurrence of polyneuritis, with the usual histological appearances in the nerve trunks.

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These symptoms (beriberi) have been observed repeatedly in epidemics in man from the use of polished rice or white bread as the chief constituent of the dietary. Deficiency of thiamine also results in cardiac dilatation and insufficiency with resultant heart failure. This condition has been designated as the "wet" type of beriberi, or as the beriberi heart. It is most commonly observed in alcoholics whose intake of the vitamin is apt to be deficient. This, as well as the polyneuritis, is not an infrequent complication of alcoholism and is due to the thiamine deficiency rather than to the toxic action of the alcohol, as formerly assumed. Improvement in such persons rapidly follows the administration of large doses of vitamin B_1 which is usually given as thiamine hydrochloride. Fifty mg. have been given daily by intravenous injection without any signs of intolerance and with rapid improvement in the condition. Thiamine deficiency is also thought to be responsible sometimes for the neuritis seen in pregnancy, alcoholism, diabetes, and pellagra.

The **effects** of a deficiency of vitamin B_1 are perhaps most satisfactorily studied by feeding pigeons on the deficient diet. Polyneuritis sets in in the course of about three weeks and soon proves fatal. The early symptoms consist of loss of appetite, weakness, lack of vigor, and constipation. Signs of impairment of nutrition of the nervous system appear later. The lack of appetite is perhaps the most characteristic of the early specific symptoms. Later on in the course of the poisoning, the nervous symptoms are prominent and consist of convulsive seizures with opisthotonus and leg weakness. Marked temperature disturbances accompany the acute nervous symptoms in pigeons, there being a profound fall of perhaps 10° or 12° F. in body temperature in a few hours. The normal temperature is regained quickly if the vitamin is furnished. Examination of the gastro-intestinal tract in pigeons and in dogs shows no marked deviation from the normal except that in severe cases in dogs there is atony of the stomach, and in pigeons late in poisoning, there is retention of food in the crop.

Mechanism and Action.—Study of the blood in thiamine deficiency shows an increase in blood sugar and in lactic acid, indicating a marked disturbance in carbohydrate metabolism. Vitamin B_1 acts in the body as a co-enzyme, co-carboxylase, which is the pyrophosphoric acid ester of thiamine and which is necessary in the chain of carbohydrate oxidation reactions of which lactic acid is the starting point. Co-carboxylase can be prepared by heating thiamine with sodium pyrophosphate and phosphoric acid. Lactic acid loses hydrogen under the influence of a dehydrogenase with the formation of pyruvic acid, and thiamine acts as a co-enzyme in the oxidative breakdown of this acid. An increase in pyruvic acid has been found in the blood, urine, and cerebrospinal fluid of cases of beriberi and in the blood of thiamine deficient pigeons and rats, and these amounts sink to normal in the cured case. The vitamin thus exerts a more or less generalized action in the body in place of one on a given organ or group of cells and places it in the category of substances involved in biological oxidations and reductions.

Crystalline vitamin B_1 hydrochloride has been adopted as the **standard**

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for this vitamin, 3 micrograms (0.003 mg.) being the International and U. S. P. units. A milligram of thiamine hydrochloride is thus equivalent to 333 U. S. P. or International units. The minimum daily requirement for an adult appears to be approximately 1 mg. with an optimal intake between 1.5 and 2.5 mg. In general the requirement is proportional to the metabolic activity, at least 0.03 mg. being necessary for each 100 Calories.

Therapeutic Uses.—Thiamine is a specific for the prevention and treatment of beriberi. It may also be of value in certain cases of anorexia which are due to some dietary disturbance. In cases of interference with proper absorption of the vitamin-containing food, the administration of concentrates may be advisable. Such conditions may arise from pernicious vomiting, from diarrhea, or from tube feeding through an intestinal fistula.

Where there is an increased excretion, larger amounts may be desirable. In cases with an increased metabolism as, for example, in fevers or in hyperthyroidism increased amounts of vitamin B_1 are necessary. In such cases 60 micrograms of thiamine hydrochloride (20 U. S. P. units) per 100 Calories should be given daily (Cowgill).

The prophylactic **dose** for an infant is 0.5 mg. and for an adult, 3 mg. However, doses of the order of 10 to 50 mg. may be advantageous in treating specific instances of thiamine deficiency.

Preparations

U. S. P.

Thiamine Hydrochloride. Small white crystals or crystalline powder, having a slight characteristic odor. Average dose, 5 mg.

Tabellæ Thiaminæ Hydrochloridi, thiamine hydrochloride tablets. Average dose, 5 mg.

For other preparations containing vitamin B_1, see pages 584 and 590.

B. P.

Aneurinæ Hydrochloridum, thiamine chloride. Dose, prophylactic, 0.3 to 0.6 mg. daily; therapeutic, 0.6 to 1.8 mg. daily.

Pulvis Vitamini B_1, an adsorbate on fuller's earth. Dose, prophylactic, 1 to 2 grams; therapeutic 2 to 6 grams.

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Riboflavin

Riboflavin, $C_{17}H_{20}N_4O_6$, another member of the vitamin B complex, was formerly known as vitamin B_2, vitamin G, or as lactoflavin. It is

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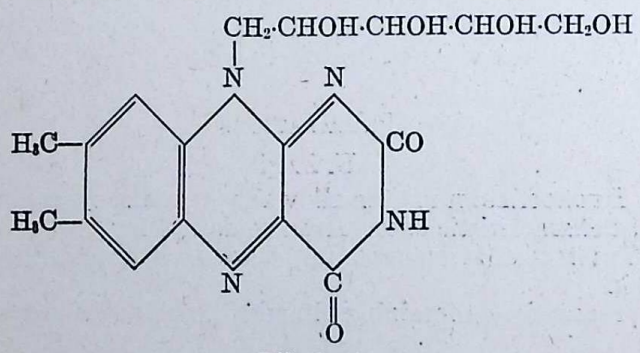
obtained as clusters of fine orange-yellow crystals which are only slightly soluble in water, giving the water a strong yellowish-green fluorescence. This greenish fluorescent pigment occurs widely distributed in nature in both the plant and animal kingdom. It is also made synthetically. It has been obtained from egg white, milk, liver, kidney, egg yolk and from such vegetable sources as dandelion blossoms, grasses, etc. The fact that the substance was obtained from these different sources was responsible for the various names which were applied to it, such as ovoflavin, lactoflavin, hepaflavin, renoflavin, etc., but when it was shown that these products were all chemically identical the designation riboflavin was adopted to cover the group. Riboflavin is apparently formed primarily in the green leaves of actively growing plants and is concentrated there in larger amounts than in other parts of the plant. Carrot tops contain about four times as much of this vitamin as do the roots. The content of this vitamin in milk is fairly uniform throughout the year in spite of the difference in feed available for the cows in winter as compared with summer, so that milk forms a dependable source of riboflavin. Liver furnishes at least ten times as much of the vitamin as does an equal weight of muscle.

Chemistry.—Riboflavin has the structural formula:



Riboflavin

It is the dimethyl derivative of iso-alloxazine combined with ribose. Its chemical designation is therefore 6,7-dimethyl-9-d-1′ribityl iso-alloxazine.

Riboflavin occurs in the animal body as a constituent of several basic enzymes. Thus, combined with protein by means of phosphoric acid, it forms the respiratory yellow enzyme of Warburg, which is present in all cells and takes part in the oxidative processes. It also is a constituent of the amino-acid oxidase and xanthine oxidase and possibly of other basic enzyme systems.

Pathology.—It has been shown that riboflavin is required for growth and maintenance of health in rats and presumably in all mammals, including man. Lack of the vitamin gives rise to the condition designated as ariboflavinosis. In man, this is characterized by **cheilosis**, fissuring at the angles of the mouth, and **glossitis**. The tongue is clean with flattened papillæ and a purplish-red or magenta discoloration. There is a seborrheic follicular **dermatitis** at the nasolabial folds and roughening of the skin (**"sharkskin"**) of the mouth and nose. There are also ocular manifestations characterized by conjunctivitis, itching, burn-

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ing, and a sensation of roughness of the eyes **(keratitis)** and photophobia. The cornea is invaded by capillaries which may be seen by examination with the slit lamp. Ultimately the vascular circumcorneal proliferation may lead to opacity. However, ariboflavinosis rarely, if ever, occurs as a clinical entity but merely as part of other avitaminotic disorders as, for example, in pellagra.

Various estimates have been made of the amounts of riboflavin necessary for normal human nutrition, and while they differ somewhat, it appears that children up to ten years of age require about 1 mg. per day and adults about 3 mg. per day.

Therapeutic Use.—Riboflavin is used as a specific in the treatment of the characteristic lesions of the tongue, lips, and face and the ocular manifestations associated with a deficiency of this vitamin. It is used also for the alleviation of symptoms of riboflavin deficiency encountered in other dietary deficiencies, particularly pellagra. In these conditions riboflavin is administered in doses of 2 to 10 mg. per day depending upon the severity of the deficiency. No toxic effects have been noted even after relatively large doses.

PREPARATIONS

U. S. P.

RIBOFLAVINUM, riboflavin, an orange-yellow crystalline powder. Dose, 5 mg.
TABELLÆ RIBOFLAVINI, riboflavin tablets. Dose, 5 mg.
For other preparations containing riboflavin see pages 584 and 590.

B. P.

RIBOFLAVINA. Dose, 0.001 to 0.01 gram.

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Nicotinic Acid (Niacin, P-P Factor) and Nicotinamide

Nicotinic acid, a third component of the vitamin B complex, occurs as white crystals which are freely soluble in water. Originally used successfully in the treatment of "black tongue" of dogs, it was very soon employed in the treatment of pellagra, a disease of man which is now recognized to be analogous to the canine disorder.

Pellagra was for many years a widespread disease characterized by dermatitis, diarrhea, and dementia. Long believed to be infectious in origin, Goldberger's classic studies proved conclusively that the disorder was nutritional in origin and due to a deficiency of the P-P **(pellagra-preventive)** factor present in yeast, fresh meats, milk, etc. Although

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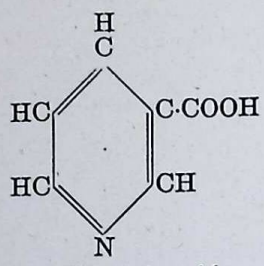
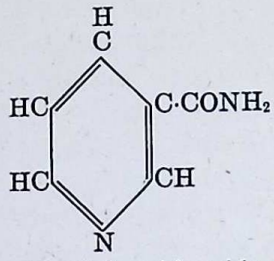
long known as a chemical entity, and in fact isolated by Funk in 1911 from rice polishings in his search for the anti-beriberi vitamin, the relation of nicotinic acid to pellagra was not demonstrated until Elvehjem in 1937 isolated it from liver concentrates and proved its effectiveness in correcting the deficiency of Goldberger's canine blacktongue-producing diet.



Nicotinic acid
(Niacin)



Nicotinic acid amide
(Niacinamide)

Chemistry.—Nicotinic acid, as shown in the accompanying formula, is pyridine carboxylic acid. It receives its name from the fact that it was first prepared by oxidizing nicotine (*cf.* page 429), the side-chain of which is replaced by COOH in this process.

The amide of nicotinic acid manifests the same therapeutic effects as does the free acid, and it is chiefly in this form that the vitamin occurs in nature. Moreover, since nicotinic acid when ingested in large doses gives rise to certain unpleasant vascular effects, the use of the amide is preferred in therapy.

Action.—Nicotinic acid has been shown to play an important rôle in the enzyme systems of the body. The amide of nicotinic acid is present in the diphosphopyridine nucleotide known as co-enzyme I or cozymase, and in the triphosphopyridine nucleotide known as co-enzyme II, both of which play an important rôle in carbohydrate metabolism.

In pellagra the administration of nicotinic acid is followed by rapid improvement in the glossitis, stomatitis, and dermatitis. When the drug is given intravenously, signs of healing may begin to appear in a few hours and the mouth lesions may be completely healed in three days. There is also a distinct improvement in the mental state of the patient within two or three days of the commencement of the treatment. Nicotinic acid has no effect upon the polyneuritis of pellagra, and it is necessary to give vitamin B_1 (thiamine) for this condition, as well as riboflavin for the associated symptoms of ariboflavinosis.

Pharmacology.—Nicotinic acid is not very toxic, but mild symptoms of intolerance may follow its administration. These symptoms which consist of severe flushing, itching, and tingling, particularly of the face, ears, and extremities, come on within a few minutes when the drug is given by mouth, but they last only from ten to twenty minutes. There is no appreciable effect on blood-pressure, temperature, or respiration. Ten milligrams given intravenously may be followed at once by these symptoms while oral doses of 50 mg. may have no unpleasant effects, although these too will sometimes be followed by symptoms. These

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effects are not observed following the administration of nicotinamide which is therefore the drug of choice particularly for parenteral use.

Following its ingestion, nicotinic acid is excreted in the urine in the form of its methyl betaine (trigonelline) and in combination with glycine (nicotinuric acid).

Therapeutic Use.—Nicotinic acid and nicotinamide are specifics for the treatment of pellagra. Their administration leads to the disappearance of the lesions characteristic of the disease, a disappearance of the porphyrinuria, and an improvement in the symptoms of the disease.

The maximum daily dose of nicotinic acid or its amide recommended for the treatment of pellagra is 500 mg. divided into ten doses of 50 mg. each. For intravenous administration a daily dose from 50 to 80 mg. dissolved in sterile salt solution is effective. One hundred milligrams dissolved in a liter of sterile salt solution and given subcutaneously has also proved efficient.

The minimum daily requirements for this vitamin are not established, but 4 to 12 mg. for children and 15 to 25 mg. for adults is recommended as the daily allowance.

PREPARATIONS

U. S. P.

ACIDUM NICOTINICUM, nicotinic acid, niacin, a white crystalline powder. Dose, 25 mg.

TABELLÆ ACIDI NICOTINICI, nicotinic acid tablets, niacin tablets. Dose, 25 mg.

NICOTINAMIDUM, nicotinamide, nicotinic acid amide, niacinamide, a white crystalline powder, freely soluble in water. Dose, 25 mg.

TABELLÆ NICOTINAMIDI, nicotinamide tablets, niacinamide tablets. Dose, 25 mg.

B. P.

ACIDUM NICOTINICUM. Dose, 0.05 to 0.1 gram.
TABELLÆ ACIDI NICOTINICI. Dose, 0.05 to 0.1 gram.
NICOTINAMIDUM. Dose, 0.02 to 0.1 gram.
TABELLÆ NICOTINAMIDI. Dose, 0.02 to 0.1 gram.

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Pyridoxine (Vitamin B_6)

This member of the vitamin B complex is also a derivative of pyridine. It is 2-methyl-3-hydroxy-4,5 hydroxymethyl pyridine. It is used in the form of the hydrochloride. Its existence was first noted by Gyorgy, who found that young rats on a controlled dietary deficiency, developed a dermatitis and acrodynia which was cured by a supplement present in yeast which he designated as vitamin B_6. This dermatitis and acrodynia

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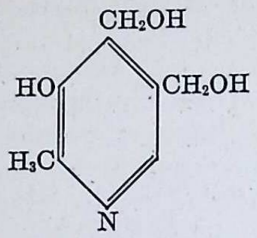
was at first believed to correspond to that observed in human pellagra and to the acrodynia seen in human infants, but this assumed relationship has been demonstrated to be in error.



Pyridoxine

Following its synthesis by Harris and Folkers in 1939 pyridoxine has been used in various clinical conditions, but its value in human disease is not clearly established. Its importance to man has been shown in cases of pellagra where certain of the symptoms of the disease were relieved by the administration of thiamine, riboflavin, and nicotinic acid, but certain other symptoms such as insomnia, irritability, weakness, and difficulty in walking occasionally remained. The administration of 50 mg. of synthetic vitamin B_6 to such cases was followed by prompt relief of symptoms with rapid increase of strength and ability to walk (Spies, Bean and Ashe). It has also been used in certain neurological and neuromuscular disorders, in the vomiting of pregnancy, and in agranulocytic angina, but its value in these conditions is not established.

The synthetic product possesses a potency equivalent to the natural product and is capable of curing the deficiency disease of rats and inducing growth when given in a single dose of 0.1 mg.

Pyridoxine is essential for the growth of excised plant roots and for certain strains of yeast, fungi and bacteria. Dogs deprived of this vitamin develop a typical microcytic hypochromic anemia. It occurs principally in the seeds of cereal grains, legumes, yeast, liver, egg yolk, meat, and fish.

The mechanism of function of pyridoxine is unknown but it is believed to be a constituent of certain enzyme systems concerned in fat metabolism.

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Pantothenic Acid

This member of the vitamin B complex was originally known as the "filtrate" and the "chick antidermatitis" factor. Because of its wide occurrence in nature it was also designated as pantothenic acid. Chemically it is N-(α,γ-dihydroxy-β-β-dimethylbutyryl)-β-aminopropionic acid.

The rôle of pantothenic acid in the human is not established. Black

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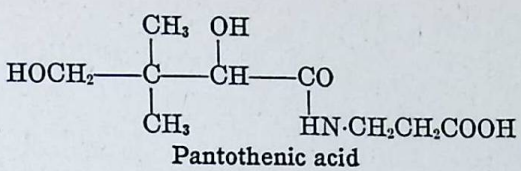
rats maintained on a pantothenic acid deficient diet turn gray, but this vitamin apparently is not the sole anti-graying factor, nor is it involved in graying of the hair in the human. Pantothenic acid is also essential for the optimal growth of certain strains of yeast and bacilli. In the chick, pantothenic acid deficiency induces dermatosis.



Pantothenic acid

The royal jelly of the honey bee is the richest known natural source of the vitamin. Yeast, liver, eggs, peanuts, and whole wheat are other good sources.

Pantothenic acid is prepared synthetically and is available in the form of the calcium salt. A study of its excretion in man indicates that 3 to 4 mg. is the daily requirement, assuming it to be an essential dietary constituent.

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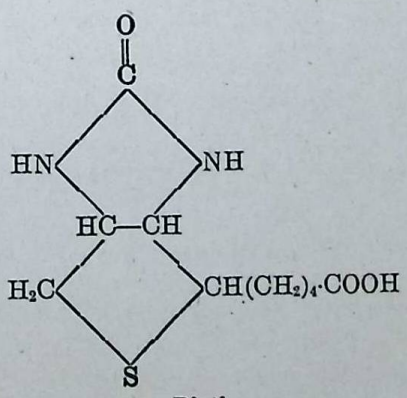
Biotin

It has long been known that the growth of yeast on synthetic media is retarded in the absence of some substance present in beerwort or in growing yeast cultures. This hypothetical substance was designated by Wildiers as bios. It was also shown that the use of egg white as the source of protein in the rat's diet gives rise to a dermatitis due to the presence of avidin, a protein which combines with a constituent normally present in the intestinal tract. This substance, which is also necessary for the growth of yeast cultures, has been isolated and synthesized and designated as biotin. It has the following structural formula:



Biotin

The action of biotin in the human is not known. It neutralizes the protective action of riboflavin against the carcinogenic action of the

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dye, "butter yellow" in rats. Attempts have therefore been made to inhibit tumor growth by feeding avidin (which prevents the formation of biotin in the intestine) without success.

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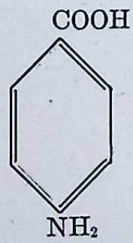
Para-aminobenzoic Acid

Normal pigmentation of the hair in the rodent, the maintenance of a normal fur coat in the rat, growth in the chick, and the multiplication of certain strains of bacteria require the presence of para-aminobenzoic acid. This substance which is present in yeast and liver extracts is therefore considered as a member of the vitamin B complex. Its rôle in the human economy is unknown.



Para-aminobenzoic acid

Para-aminobenzoic acid has been used recently in the treatment of diseases caused by **Rickettsia.** Encouraging results have been obtained in the treatment of experimental tsutsugamushi disease (scrub typhus), louse-borne typhus, and Rocky Mountain spotted fever. The drug has also been used in the human with promising results.

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Inositol

Inositol occurs in plants in the form of a calcium magnesium phosphoric acid combination known as phytin and in muscle (muscle sugar). It is an essential dietary factor of the vitamin B complex. Its deficiency affects the growth and hair of the mouse, induces "spectacled eye" in the rat, and prevents normal growth in the chick. It is also essential for the growth of certain yeasts and bacteria.

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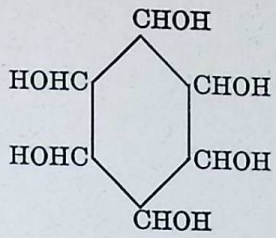
Inositol occurs in animal tissues, fruits, and vegetables. It is believed to exert lipotropic activity, but this is questionable. No clinical disorders in the human have been associated with a deficiency of inositol.



Inositol
(Hexahydroxycyclohexane)

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MCHENRY AND PATTERSON: Physiol. Revs., **24**, 128, 1944.
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Choline

This constituent of lecithin is also considered as a member of the vitamin B complex. It has already been discussed in an earlier section (page 444). Its absence from the diet causes perosis in chicks, a condition in which there is abnormal shortening and thickening of the bones and slipping of the tendons. It also stimulates growth in turkeys, chicks, and dogs. A deficiency of choline in the diet of the mammal also gives rise to fatty degenerative states in the liver and kidney.

Choline appears to play a rôle in transmethylation, that is, in the transfer of methyl groups, in the body.

Choline has been used in the treatment of **cirrhosis** of the liver and hepatitis with promising results. It is administered in the form of the hydrochloride in aqueous solution or in the form of tablets of organic acid salts in doses of one gram six times daily. **Methionine** plays a similar rôle and has also been used in place of or in conjunction with choline.

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Folic Acid

Several strains of bacteria require the presence of a constituent present in liver, kidney, and yeast which because of its presence also in green leaves was designated as folic acid (*folium*, a leaf). This vitamin has also been designated as the *L. casei* factor because it is essential for the

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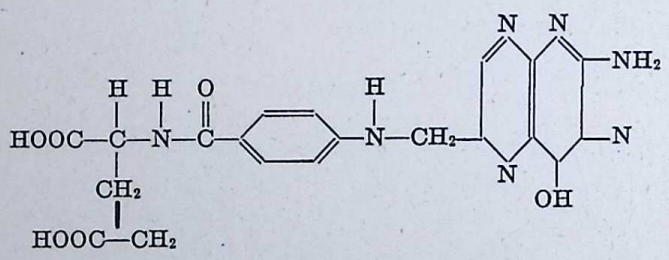
growth of *Lactobacillus casei* and *S. fæcalis R.* It has also been designated as vitamin M because its deficiency causes a retardation of growth, anorexia, and leukopenia in the monkey. In the chick, a macrocytic hypochromic anemia results from its deficiency. "Vitamin Bc" as a factor required by the chick was originally designated, "Vitamin M," the factor needed by the monkey, "factors R, S and U" and the "morite eluate factor" of vitamin B complex are now accepted as identical with folic acid.

Folic acid has been prepared synthetically, and is available commercially in tablets for oral and in aqueous solution in ampoules for parenteral administration. As shown in its accompanying formula, folic acid is pteroylglutomic acid. It has been used in the treatment of the anemia of tropical sprue, nutritional macrocytic anemia, pernicious anemia, and other forms of macrocytic anemia with claims of success (Spies). Its use in leukopenia has also been suggested (Watson *et al.*). It is administered in doses of 5 to 20 mg. daily in divided doses orally or when necessary by intramuscular injection.



Folic Acid (pteroylglutomic acid)

REFERENCES

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Vitamin Bc

In addition to folic acid and vitamin Bc the presence of two other members of this group have been demonstrated. These are designated as vitamin B_{10} which is necessary for normal feathering and vitamin B_{11} which is necessary for normal growth in chicks.

Ascorbic Acid (Vitamin C, Cevitamic Acid)

Scurvy has been recognized for many centuries as a disease which was common among sailors, explorers, and others whose dietary was deficient in fresh fruits, meat, and vegetables. The antiscorbutic activity of limes led to its adoption early in the British Navy.

Szent-Györgyi, searching for a respiratory enzyme, first isolated ascorbic acid from concentrates of the adrenal cortex. Its structure was elucidated by Haworth, who showed that it was a lactone related to gulonic acid. Svirbely and Szent-Györgyi, and Waugh and King in 1932 showed that the compound was identical with vitamin C, the antiscorbutic vitamin. Reichstein's synthesis of the compound made possible the commercial preparation of the vitamin on a large scale.

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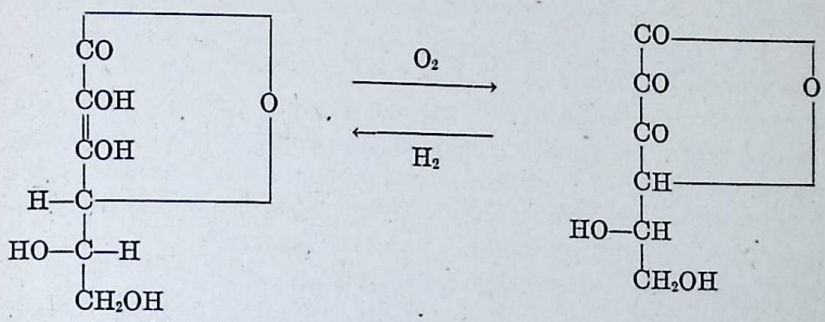
Chemistry.—Ascorbic acid, $C_6H_8O_6$, is a relatively simple chemical compound related to the sugars. It readily undergoes reversible oxidation, being converted in this process to dehydro-ascorbic acid, which in turn may be reduced to the original ascorbic acid. It may thus be titrated with 2,6-dichlorophenol-indophenol, a blue dye, in alkaline solution, the dye being converted to the reduced colorless form. This reaction is used for the chemical assay of the vitamin and for its determination in blood, urine, or other body fluids.



Ascorbic acid — Dehydroascorbic acid

Ascorbic acid is optically active, the levo compound constituting the vitamin; the dextro body is practically inactive. Vitamin C is quite unstable and is destroyed by prolonged boiling, especially if the reaction of the material is neutral or alkaline. In acid media (such as occurs in tomatoes) the destruction is slower, but about 50 per cent is said to be destroyed by boiling for one hour. In the form of preserved foods it undergoes slow destruction, but many factors, such as the reaction and presence of oxygen, may greatly modify the rate at which it disappears. Some of the vitamin is destroyed by the ordinary methods of cookery and preservation, and a diet apparently containing a fair amount of vegetable food may be rendered insufficient through the methods of preparation and storage.

Occurrence.—Ascorbic acid is found in growing plants but is mainly supplied in the form of potatoes, fruits, and fresh green vegetables. Potatoes do not contain large amounts, but on account of the large quantities of this vegetable which are eaten they furnish an important source of this vitamin. It is most abundant in the juice of oranges, lemons, and tomatoes. It is present in high concentration in the adrenal cortex (one mg. per gram of tissue), from which it was first isolated, as well as in other tissues (ovary, pituitary). Paprika is unusually rich in the vitamin, and the first large-scale production was from this source. Rose hips and fir needles also contain large amounts. The average vitamin content of orange juice is 0.6 to 0.7 mg. per cc. and of lemon juice 0.47 mg. per cc. Dried grains and seeds contain only traces, but if they are allowed to germinate, the vitamin is developed, and in case of necessity growing malt or peas may be used to supply it. The most convenient method of transporting it is in the form of lemon juice, which retains its activity for a long time, even when dried. Orange juice powder or the juice itself, if it is saturated with carbon dioxide gas, will retain its vitamin potency for long periods. Canned tomatoes are also a very important source of this vitamin. Like thiamine, it is not stored in the tissues, and a more regular supply is necessary than of vitamin A.

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Pathology.—Deficiency in vitamin C leads to malnutrition with loss of weight and culminates in the symptoms of scurvy, which was formerly prevalent in long sea voyages when fresh vegetables were unobtainable, and which still occurs occasionally in urban populations from neglect and ignorance of the value of fresh vegetable food. In scurvy the chief lesions begin along the alimentary canal, and apparently arise from injury to the capillaries and arterial walls which leads to exudations and hemorrhages. There is soreness and stiffness of the joints. The gums are painful and hyperemic and the teeth become loose. These changes appear in the guinea pig readily, and this animal is most suitable for the investigation of deficiency of vitamin C.

The vitamin is excreted in the urine in amounts which under ordinary circumstances are remarkably constant, but if excessively large amounts are taken, the curve of excretion rises sharply to a maximum which is reached in about three hours, after which the amount excreted decreases rapidly to reach the normal level in a day or two.

It is probable that the average adult requires at least 50 to 75 mg. of vitamin C daily and that a child requires about 40 mg. and an infant 30 mg. daily. In pregnancy and lactation the daily requirement may be as high as 100 or 150 mg. Also in infections, the requirement may be high.

Vitamin P.—Szent-Györgyi isolated from Hungarian paprika and lemon juice a substance which he believed controls vascular bleeding. The substances responsible for the action were isolated and shown to be glucosides of two flavones designated as hesperidin. The status of hesperidin as a vitamin is still disputed, and its use clinically for the control of hemorrhagic tendency seen, for example, in hypertension, is still in an experimental stage.

Rutin, a flavonol glucoside, which occurs in buckwheat plants, has been used as a source of this anti-hemorrhagic factor.

Therapeutic Uses.—Ascorbic acid is a specific for the prevention and cure of scurvy. Early or latent scurvy may occur due to inadequate diet or to improper absorption of the vitamin, in which case the administration of the vitamin in some form is indicated.

It has been claimed that various other conditions may result from lack of an adequate amount of vitamin C, but convincing evidence in favor of such views is lacking, and the prescription of vitamin C in such states is not indicated unless they can be definitely shown to result from such a deficiency. Among the conditions for which such claims have been made are dental caries, anemia, malnutrition, anorexia, and various forms of infections. Vitamin C, like vitamin A, has been designated by some as an "anti-infective" vitamin, but while infections may occur in any condition of avitaminosis or malnutrition, it has not been shown that these vitamins can directly affect infective processes or act as an aid in preventing such infections.

The healing of wounds is delayed in the presence of vitamin C deficiency. The vitamin is, therefore, often prescribed in patients following surgical operations in whom there is a possibility of an inadequate dietary intake of this vitamin.

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The therapeutic dose of ascorbic acid for infants is 30 to 50 mg. daily; the protective dose, 10 mg. daily. For adults the respective doses are 100 to 150 mg. and 25 mg. There is no evidence for any detrimental effects from even massive doses (10 grams).

Preparations

U. S. P.

Acidum Ascorbicum, ascorbic acid, vitamin C, white or slightly yellow crystals or powder; readily soluble in water; stable in dry state but deteriorating in watery solutions. Dose, 50 mg.

Tabellæ Acidi Ascorbici, ascorbic acid tablets, vitamin C tablets. Dose, 50 mg.

B. P.

Acidum Ascorbicum. Dose, prophylactic, 25 to 50 mg.; therapeutic, 100 to 250 mg., daily.

Tabellæ Acidi Ascorbici. Doses as in preceding.

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Vitamin D

Often spoken of as the antirachitic vitamin, vitamin D is found in abundance in cod-liver oil, halibut-liver oil, other fish liver oils, in egg yolk, milk, and butter. Being fat-soluble, it was for a time classified with the other vitamins having similar characteristics in this respect.

Its importance lies in its use as a prophylactic and cure for rickets in children and osteomalacia in adults. In rickets, there is a disturbance of the mineral metabolism so that calcification of the bones does not take place normally. The rachitic infant stores less calcium and inorganic phosphorus than does a normal child, and does not utilize the calcium phosphate normally in the process of ossification. An early sign of the disease is an increase in the alkaline phosphatase level of the blood. There is also a low concentration of inorganic phosphorus in the blood, and in severe cases the blood calcium may also be reduced somewhat below the normal level. When vitamin D is administered there is a prompt increase to normal, the vitamin apparently controlling the concentration of both calcium and phosphorus in the blood and their deposition in the bones. In osteomalacia there is a loss of calcium phosphate from the skeleton which results in softening of the bones and deformity.

Chemistry.—The knowledge of the relation of this vitamin to cholesterol has been gradually evolved. It was early shown that it was the non-saponifiable portion of the oil which was active, and this portion

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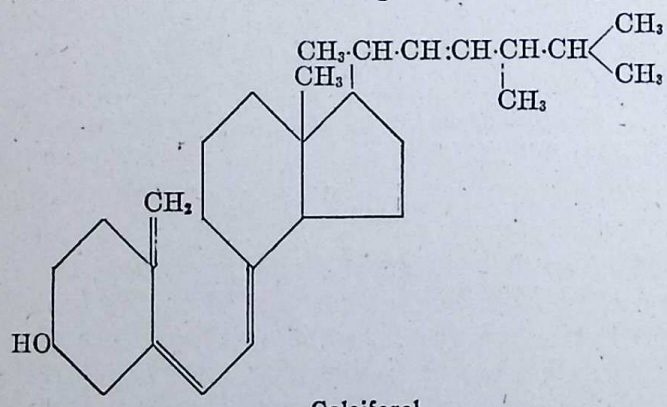
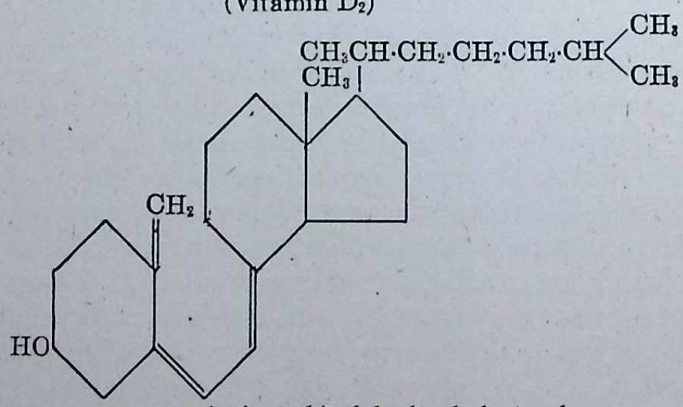
included the sterol, cholesterol, or, in the case of vegetable oils, the similar body phytosterol.

The fact that the curative effects of cod-liver oil in rickets could also be obtained by exposure of the body to direct sunlight or to the ultra-violet rays from a quartz lamp suggested the possibility that vitamin D was formed by activation by light of some constituent, possibly cholesterol, present in the skin. However, it was found that although crude preparations of cholesterol when irradiated showed vitamin D activity, highly purified cholesterol when similarly treated remained inert. The vitamin D formed by irradiation was a result of the presence of ergosterol, a sterol first found in ergot and present in yeast, which becomes highly antirachitic when irradiated.

It is now known that several related compounds possess antirachitic activity. Irradiation of ergosterol results in the formation of the antirachitic mixture known as **viosterol.** The pure crystalline compound responsible for the antirachitic activity is **calciferol**, or vitamin D_2. In addition to calciferol, irradiation of ergosterol results in the formation of a series of other products—lumisterol, tachysterol, toxisterol, etc. It is the presence of certain of these by-products, some of which are highly toxic, that led to some of the unfortunate harmful effects noted soon after the introduction of irradiated ergosterol in therapeutics.



Calciferol
(Vitamin D_2)



Activated 7-dehydrocholesterol
(Vitamin D_3)

A second compound possessing marked antirachitic activity is derived by irradiating 7-dehydrocholesterol, which is prepared from cholesterol.

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This compound, like ergosterol, is also a provitamin D and is responsible for the antirachitic activity which follows irradiation of the skin and certain food products It is designated as vitamin D_3, and as shown in the accompanying formulæ, is closely related to calciferol, of which it is the demethyldihydro-derivative.

Vitamin D_1 was the designation originally given to a lumisterol-calciferol mixture mistaken for the pure vitamin. Vitamin D_4 is activated 22-dihydroergosterol and is dihydrocalciferol. 7-dehydrositosterol also possesses antirachitic activity following irradiation as do also a number of other sterol derivatives, but these are of little importance therapeutically.

The vitamin D of fish oils appears to be a mixture consisting principally of vitamin D_3.

The effectiveness of sunlight and ultraviolet light in the prophylaxis of vitamin D deficiency resides in the fact that the provitamins present in the skin are converted to the active vitamins. Irradiation of yeast, milk, and other foods also render these antirachitic due to the presence of provitamins. By ingestion of irradiated yeast or other foodstuffs of cows, the vitamin D formed in this way passes into the milk, which shows high antirachitic activity.

Distribution.—Vitamin D is not widely distributed in the animal kingdom, fish-oil being perhaps its most important natural source. Fish which contain much body oil, such as salmon, sardines, and herring, are rich natural sources of the vitamin. The yolk of eggs is also an excellent source, and it is not destroyed by boiling or by storage. Milk and butter do not contain much vitamin D unless the cows from which they are derived are fed irradiated foodstuffs. Living plant tissues such as leafy vegetables probably contain no vitamin D. Exposure to the sunlight serves as the principal method whereby the organism obtains its requirement for the essential vitamin. Persons who do not expose themselves to the light (as among the Moslems who practice Purdah) are for this reason liable to suffer from osteomalacia, the form in which avitaminosis D affects the adult. Even where the diet is deficient in vitamin D, exposure to sunlight, as among the laborers of the Orient, prevents the appearance of the disorder.

Toxicity.—Excessive amounts of vitamin D lead to a condition of hypervitaminosis. With moderate overdosage there is a fall in the amount of calcium and phosphate in the intestinal contents and an overcalcification at the growing ends of bone. The latter condition is ascribed to the excessive calcium and phosphorus in the blood and the action of the phosphatase or calcifying enzyme. In severe poisoning with this vitamin the calcium and phosphate may be drawn from the bones in spite of the overcalcified epiphyses, and there may be a net loss of mineral salts in the bones. Abnormal deposition of calcium in the blood-vessels and soft tissue has also been described after the administration of excessive doses of certain artificially prepared concentrates containing vitamin D. More recent work indicates that the toxicity observed in earlier work was due to the presence of impurities in irradi-

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ated mixtures. There is a wide margin of safety in the use of purified preparations and entire safety in the use of natural preparations.

Therapeutic Use.—Exposure to sunlight remains for the adult the chief means for avoiding avitaminosis D. The routine prophylactic administration of some form of vitamin D, as fish oil, viosterol, or calciferol, is advocated for children. Vitamin D is a specific for the cure of rickets and osteomalacia. The use of some vitamin D preparation is also advocated during pregnancy, since the demand for the vitamin is increased by gestation.

The recommended daily allowance of vitamin D for children, and during pregnancy, is 400 to 800 international units, the latter being defined as equivalent in activity to 0.025 micrograms of crystalline vitamin D_2. Premature infants require large doses (1,000 units). For the treatment of rickets and osteomalacia the administration of 5,000 units daily are advocated. In certain cases of "refractory" rickets in which the normal response to vitamin D therapy is not observed, massive doses may be required. However, when using doses greater than 20,000 units daily for infants or 50,000 units for a child, weekly determinations of the blood calcium level should be made since vitamin D in large doses may raise the blood calcium to toxic levels.

The value of massive doses of vitamin D in chronic arthritis and in allergic disorders has not been demonstrated. The efficacy of the vitamin in the treatment of psoriasis is also not established.

The use of dihydrotachysterol, a compound related to vitamin D_2 in hypoparathyroidism, has already been described on page 552.

Preparations

U. S. P.

Oleovitamina D Synthetica, viosterol in oil, a solution of synthetic vitamins D_2 or D_3 and dissolved in a vegetable oil and standardized so as to contain not less than the equivalent of 10,000 U. S. P. vitamin D units in each gram. Dose, prophylactic, 0.1 cc.

For other preparations containing vitamin D see pages 584 and 589.

B. P.

Calciferol, viosterol. Dose, prophylactic, 0.025 to 0.05 mg.; therapeutic, 0.05 to 0.075 mg.

Liquor Calciferolis. Dose, prophylactic, 0.3 to 0.6 mil.; therapeutic, 0.6 to 1 mil.

Liquor Vitamini D Concentratus. Dose, 0.03 to 0.2 mil.

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α-Tocopherol (Vitamin E)

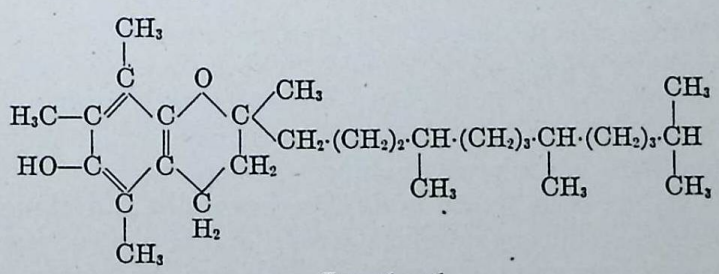
Evans and his co-workers found that when rats were fed on synthetic food mixtures with the proper mineral constituents added and vitamins A and B the animals would grow and appear to be perfectly normal, but they sooner or later showed complete sterility. The sterility is due to a deficiency in the diet of certain natural foods containing vitamin E, and it can be cured by giving these foods or by giving concentrated extracts of the foods. In the male there are changes in the germ cells passing on in severe cases to loss of the seminiferous epithelium, while in the female there is death and resorption of the developing embryos. The growth of the embryos seems to be normal for a time, but about the eighth day there is retardation in development, and fetal deaths occur about the twelfth day, although there is considerable variation in this respect. If to such a female vitamin E be given, either in the form of the proper food or as an extract, the next generation may result in a normal vigorous litter.

Occurrence.—Vitamin E is found to a certain extent in animal tissues such as the muscles, fat and the viscera, but it is not present in large amounts. Milk fat also contains little, and cod-liver oil is almost lacking in it. On the other hand, it is found in some concentration in plants, especially in seeds and green leaves. Considerable amounts have been found in egg yolk and liver. The richest source is found in wheat germ oil.

Chemistry.—Emerson and Evans isolated from the non-saponifiable fraction of wheat germ oil several related compounds which manifested vitamin E activity and which proved to be derivatives of chromane. The most potent of the compounds was an alcohol designated as α-tocopherol (*tokos*, childbirth; *phero*, to bear) and which is now considered to be vitamin E.

Vitamin E, as seen in the accompanying formula, is a hydroxymethyl derivative of chromane with a phytol side-chain. It is prepared synthetically by condensation of phytol with methylhydroquinone.

Other closely related compounds (β- and γ- tocopherol) also possess some vitamin E activity.



α—Tocopherol

Therapeutic Use.—Although originally discovered by its relation to sterility, vitamin E deficiency was subsequently found to exert other effects as well in the experimental animal. Thus, rabbits and guinea pigs, as well as rats and dogs, on a vitamin E deficient diet develop dystrophy and atrophy of the voluntary muscles. In the rabbit there

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is also a decrease in the creatine content of the muscles, with an increase in the urinary output of creatine. Chicks on a vitamin E deficient diet develop encephalomalacia (softening of the brain).

Insofar as the human is concerned, the indications for the use of vitamin E remain undefined. There is no conclusive evidence to indicate that it is useful in cases of sterility or repeated abortion, nor is its value in neuromuscular dystrophies and other degenerative nerve disorders established.

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Vitamin K

In 1935 Dam observed that chickens which were fed upon a diet deficient in certain fat-soluble substances, but adequate in other respects, suffered from a fatal hemorrhagic condition in which bleeding occurred not only from the pin-feathers but also into the subcutaneous tissues and muscles. This condition, which was due to a decrease in prothrombin in the blood, could be controlled by the administration of the non-saponifiable fraction of hog-liver fat, by putrefied fish meal, or by feeding alfalfa, cabbage, etc. The protective factor concerned was named the "Koagulation vitamin," or vitamin K.

This vitamin, or substances allied to it, is found widely distributed in nature, especially in the vegetable kingdom. It is present in alfalfa, spinach, kale, carrot tops, tomatoes, and in certain vegetable oils such as soybean oil. It is also formed from fish meal under the action of bacteria which are capable of synthesizing the vitamin. Of great importance is the synthesis of this vitamin by the bacteria in the lower portion of the intestinal tract, as shown by Almquist and Stokstad. Absorption from this portion of the intestine is minimal in the chicken but is usually adequate in mammals, so that they are not likely to suffer from this form of avitaminosis unless there is faulty absorption from the intestine or some form of liver impairment which may interfere with the synthesis of the prothrombin.

Action.—It has been shown both experimentally and clinically that the hemorrhagic tendency in biliary fistulæ and in obstructive jaundice is due to a deficiency of prothrombin in the blood. The feature common to these two conditions is lack of bile in the intestine, which prevents the absorption of vitamin K. In the absence of bile even massive doses of vitamin K administered orally are frequently inadequate to restore the blood coagulation time to normal. In vitamin K deficiency, prothrombin is not formed by the liver and the coagulation time of the blood is prolonged.

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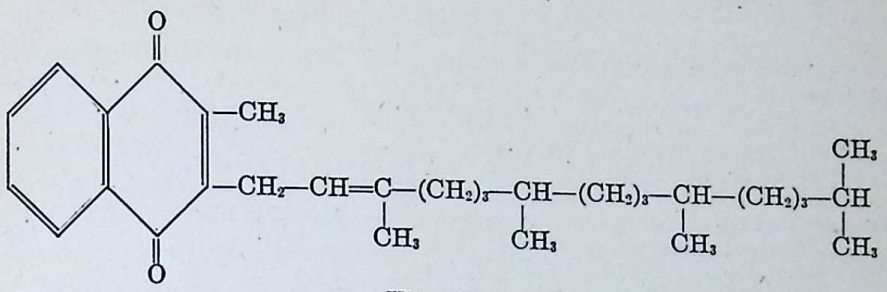
Chemistry.—Vitamin K_1 as found in alfalfa differs from its vitamer present in putrefied fish meal (vitamin K_2). The two compounds have the same ring structure, 2-methyl, 1, 4-naphthoquinone, but differ slightly in the side chain attached to carbon 3. As shown in the accompanying formula, vitamin K_1 is 2-methyl-3-phytyl-1, 4-naphthoquinone.



Vitamin K_1

1, 4-Naphthoquinone itself also shows vitamin K activity which is greatly enhanced by the introduction of a methyl group. The latter compound, known as **menadione**, is about three times as active as vitamin K_1 or K_2 and being easily prepared synthetically is the chief form in which vitamin K is available for clinical use. It is available in the form of tablets and in oil solution for oral administration. A solution in oil is also available for intramuscular injection. Combinations of menadione with sodium bisulfite are soluble in water and may be administered also intravenously when necessary.

Therapeutic Use.—Vitamin K is used in cases of obstructive jaundice and in patients with biliary fistulæ where there is a tendency to hemorrhage due to a deficiency of prothrombin in the blood. Prothrombin deficiency may, however, result not only from the improper absorption of vitamin K from the intestine but also from the inability of the liver to utilize the vitamin in the formation of prothrombin. Following the administration of vitamin K in obstructive jaundice there is an increase in prothrombin, a shortening of prothrombin time, and recovery from the hemorrhagic tendency.

Vitamin K preparations have also been used in other conditions in which there is an interference with absorption from the intestine, in women during labor as a prophylactic against the occurrence of hemorrhage in the newborn, and in the treatment of the physiological hypothrombinemia of the newborn. It is also used as an antidote to counteract the effect of drugs (*e. g.*, salicylates) which depress the prothrombin content of the blood.

Vitamin K may be administered by mouth and also by injection. In patients with obstructive jaundice, and, therefore, lacking bile in the intestine, the oral administration of the vitamin should be accompanied by the use of bile itself or of bile salts. Water-soluble preparations, however, do not require the concomitant administration of bile salts.

Vitamin K and menadione are administered in doses of $\frac{1}{2}$ to 2 mg. daily. In cases of overdosage with dicumarol the administration of large doses of the vitamin are recommended (*cf.* p. 581).

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PREPARATIONS

U. S. P.

MENADIONI SODII BISULFIS, menadione sodium bisulfite, a white, crystalline powder soluble in water. Dose, 2 mg.

INJECTIO MENADIONI SODII BISULFITIS, menadione sodium bisulfite injection, a sterile solution in water. Dose, 2 mg., parenterally.

B. P.

MENAPHTHONUM, menaphthone, menadione. Dose, 0.005 to 0.01 gram, intramuscularly.

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K. THE DIGITALIS SERIES

The digitalis series embraces a considerable number of substances which are characterized by their action on the heart. They are widely distributed in the vegetable kingdom in very different botanical families and have long been in use for various purposes in civilized and uncivilized countries. Some of them were employed as remedies by the laity long before their virtues were recognized by the medical profession, while others have been used as arrow poisons and ordeal poisons by the natives of different parts of Africa and the Eastern Archipelago.

The most important plants which contain bodies belonging to this group are *Digitalis purpurea* (purple foxglove) and *Digitalis lanata*, *Strophanthus hispidus*, or *Kombé*, and *Scilla maritima* (squills). Others which are less frequently used are *Helleborus niger* (Christmas rose), *Convallaria majalis* (lily of the valley), *Apocynum cannabinum* (Canadian hemp), and *Adonis vernalis* (pheasant's eye). Similar effects are obtained from bodies contained in other species of these genera and in a large and ever-growing list of other plants, such as *Antiaris* (Upas tree), *Nerium* (oleander), *Acocanthera* (ouabaio), *Erythrophlœum* (sassy bark or Casca bark), *Thevetia*, *Cheiranthus*, *Periploca græca*, and *Coronilla*. Numbers of other plants resemble digitalis in their effects, and moreover these bodies are not confined to the vegetable kingdom, for Faust, Abel, and Chen and his co-workers have isolated from various species of toads substances which induce the same changes in the heart. Salts of barium also induce many of the changes characteristic of this series.

History.—The cardiac glycosides have been used from time immemorial principally because of their toxic effects. Strophanthus, for example, is still used by primitive tribes to prepare arrow poisons. Squill is mentioned in the Ebers papyrus (1500 B. C.) and was used by the ancient Egyptians in many illnesses. William Withering, in 1785,

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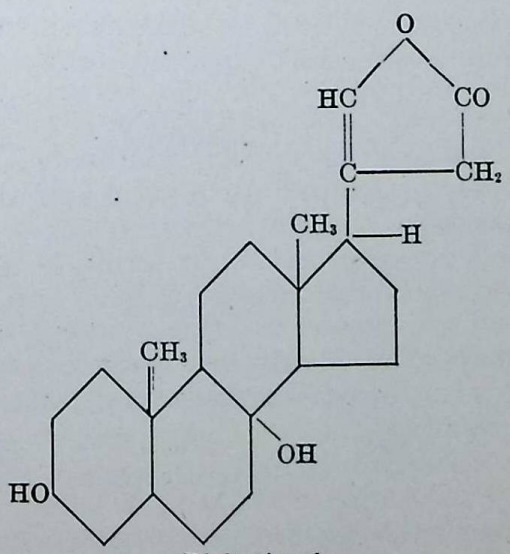
first introduced the use of digitalis in his classic monograph, "An Account of the Foxglove and Some of its Medical Uses: with Practical Remarks on Dropsy, and Other Diseases." He was led to his discovery by investigating the remarkable effects obtained by an old woman in the treatment of dropsy. Withering found the beneficent effects to be due to the presence of digitalis among the sundry herbs which the "old woman of Shropshire" used in her treatment.

Because of the lack of information regarding the mechanism of action of digitalis, and because of its toxic effects when used indiscriminately, the use of the drug gradually fell into disrepute until MacKenzie, in 1905, reëstablished the correctness of Withering's teachings. Recent physiological studies have elucidated the mechanism of its action in human disease. Many of the active principles derived from the digitalis bodies have been isolated and made available in pure form for clinical use, thereby giving a much broader field of application of the drugs as well as permitting more exact dosage and control than is possible with crude preparations.

Chemistry.—In the study of the chemistry of digitalis bodies the main difficulties have arisen from the fact that in many cases more than one active principle is present; that they are present in only very small quantities; that all have a very complex structure; and the fact that unless special precautions are taken, enzymatic processes alter the compounds naturally present in the plant.

Almost all are glycosides which on treatment with acids are hydrolyzed, breaking up into non-carbohydrate constituents the so-called "aglucones" or "genins", and sugars which, in some cases, possess unusual character. Many of the aglucones are chemically very closely related and possess the same number (23) of carbon atoms. They are hydroxylactones of sterol hydrocarbons in which one hydroxyl group is connected with a sugar molecule or chain of several sugars to form the glycoside. The structure of a typical aglucone is given in the accompanying formula for digitoxigenin.



Digitoxigenin

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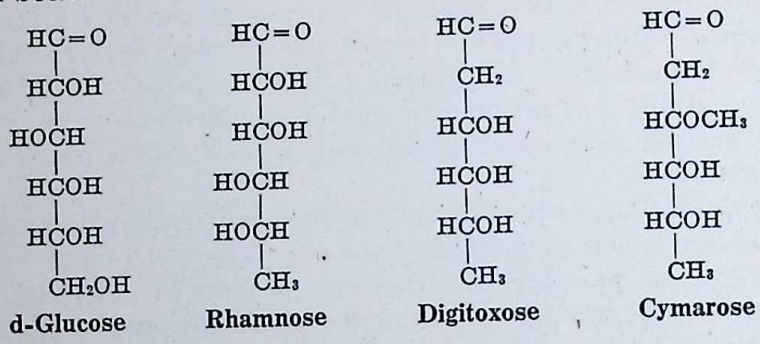
The differences between the various aglucones are due in the main to the number, arrangement, and function of the oxygen atoms present in the molecule. The interest and importance of these aglucones consist in the fact that it is in this portion of the glycosidal molecule that the characteristic cardiac action resides.

The sugar portion of the cardiac glycosides, while itself inert, apparently through its union with the aglucone gives the special character to the molecule which affects its absorption and transport in the organism and so influences its specific affinity for cardiac muscle. Several of the sugars, *e. g.*, digitoxose, cymarose, sarmentose and digitalose have thus far been found to occur naturally only in the cardiac glycosides.



Some simple sugars of the cardiac glycosides

The distribution of the cardiac glycosides in the plant varies in different species. In the case of *digitalis*, the leaves and seeds are utilized; in *strophanthus*, the seeds; in *squill*, the bulbs; in *Convallaria*, the flowers; and in *ouabaio*, the wood and bark. In addition, there are saponin bodies which do not show the typical digitalis effect on the heart but which are extracted along with the glycosides which possess the cardiac actions.

Three glycosides—digitoxin, gitoxin, and gitalin—have been isolated in pure state from the leaves of digitalis purpurea. Digitoxin, on hydrolysis with acids, forms one molecule of digitoxigenin (the aglucone of the glycoside) and three molecules of digitoxose (a sugar).

$$\underset{\textbf{Digitoxin}}{C_{41}H_{64}O_{13}} + 3H_2O = \underset{\textbf{Digitoxigenin}}{C_{23}H_{34}O_4} + \underset{\textbf{Digitoxose}}{3C_6H_{12}O_4}$$

Gitoxin, on hydrolysis, forms three molecules of the same sugar, digitoxose, and gitoxigenin.

$$\underset{\textbf{Gitoxin}}{C_{41}H_{64}O_{14}} + 3H_2O = \underset{\textbf{Gitoxigenin}}{C_{23}H_{34}O_5} + \underset{\textbf{Digitoxose}}{3C_6H_{12}O_4}$$

Gitalin, on hydrolysis, forms only two molecules of digitoxose and gitoxigeninhydrate, which by dehydration forms gitoxigenin.

$$\underset{\textbf{Gitalin}}{C_{35}H_{56}O_{12}} + 2H_2O = \underset{\textbf{Gitoxigeninhydrate}}{C_{23}H_{36}O_6} + \underset{\textbf{Digitoxose}}{2C_6H_{12}O_4}$$

The glycosides thus far isolated from the seeds of digitalis purpurea differ from those occurring in the leaves. As early as 1875 Schmiede-

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berg isolated a crystalline body from the seeds which he designated as *digitalinum verum*. This glycoside has the formula $C_{36}H_{56}O_{14}$. Its primary aglucone is gitoxigenin, which is combined with digitalose and glucose to form the original glycoside.

Recently Stoll and Kreis, employing a special technique which avoided enzymatic cleavage, succeeded in isolating two new glycosides from digitalis. These correspond to digitoxin and gitoxin, but both contain an additional glucose molecule and are designated Purpurea glycoside A and B. If these glycosides are subjected to the action of an enzyme obtained from the leaves, they undergo hydrolysis, forming in the case of A, digitoxin and glucose, while B forms gitoxin and glucose.

$C_{47}H_{74}O_{18}$	+	H_2O	=	$C_{41}H_{64}O_{13}$	+	$C_6H_{12}O_6$
Purpurea glycoside A				**Digitoxin**		**Glucose**
$C_{47}H_{74}O_{19}$	+	H_2O	=	$C_{41}H_{64}O_{14}$	+	$C_6H_{12}O_6$
Purpurea glycoside B				**Gitoxin**		**Glucose**

From **Digitalis lanata** a number of crystalline glycosides have been obtained which as a group have been designated "digilanid." This, however, consists of a mixture of three isomorphous closely related substances, the digilanids or lanatosides A, B, and C in the approximate proportions of 47 per cent digilanid A, 16 per cent B, and 37 per cent C. The formula assigned to digilanid A is $C_{49}H_{76}O_{19}$; digilanid B is $C_{49}H_{76}O_{20}$; and digilanid C is $C_{49}H_{76}O_{20}$. These glycosides yield, in addition to the aglucone and the carbohydrate, a molecule of acetic acid, a substance which had not previously been encountered as a constituent of digitalis glycosides. The close relationship of these glycosides to the glycosides of digitalis purpurea is shown by the fact that by means of the enzymes present in the leaves digitoxin is obtained from digilanid A, gitoxin from digilanid B, and digoxin from digilanid C. Purpurea glycoside A of the official digitalis is said to be identical with deacetyldigilanid A and purpurea glycoside B with deacetyldigilanid B, the purpurea glycosides being obtained by the removal of the acetyl group from the corresponding digilanids (Stoll).

The active principles of the different species of Strophanthus have been studied by Jacobs and his co-workers. These principles also have been shown to be glycosides which break up in the same manner into aglucones and sugars. In Strophanthus kombé there are several active glycosides, all being derivatives of one aglucone, strophanthidin ($C_{23}H_{32}O_6$). One of these substances, cymarin, $C_{30}H_{44}O_9$, has been shown to be a glycoside of strophanthidin and a sugar, cymarose. The other glycosides are combinations of cymarin with one or more molecules of glucose and can be enzymatically cleaved to cymarin and glucose. K-Strophanthin, which is the main specific constituent of kombé seeds, is a mixture of water-soluble glycosides in which cymarin is combined with two or more molecules of glucose.

Strophanthus hispidus also contains cymarin as a constituent of a mixture of glycosides, in which it occurs free and mostly in combination with glucose. In the latter case these complex glycosides exist as a

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water-soluble amorphous mixture from which cymarin has been obtained by enzymatic cleavage.

From **Strophanthus gratus** a crystalline glycoside, **ouabain**, has been obtained. It was so named as it was first isolated from the root and bark of the Ouabaio tree which is used as a source of an arrow poison by the Somalis of East Africa. *Ouabain*, $C_{29}H_{44}O_{12}$, is one of the most important glycosides of this group. Because of its well-defined physical characteristics and crystalline structure it served for a time as a standard in the United States for the assay of the digitalis group of drugs.

From **Periploca græca**, a plant indigenous to the Black Sea districts, a crystalline glycoside ($C_{36}H_{56}O_{13}$), periplocin, has been isolated. This glycoside is a combination of glucose with a similar glycoside, periplocymarin ($C_{30}H_{46}O_8$). This in turn yields, on hydrolysis, an aglucone, periplogenin, and the sugar, cymarose.

Antiaris toxicaria, the upas tree of the Malayan Archipelago, yields two glycosides, α and β-antiarin, which, on hydrolysis, yield the same aglucone, antiarigenin, but different sugars.

From **Scilla maritima** or Squills, a crystalline glycoside, scillaren A ($C_{36}H_{52}O_{13}$), has been isolated as well as an amorphous glycoside, scillaren B, which may be a mixture. Scillaren A yields an aglucone, scillaridine, and a sugar. In certain of its chemical reactions the aglucone scillaridine differs from the aglucones of the digitalis-strophanthus group (Stoll).

From **Thevetia neriifolia** a cardiac glycoside, thevetin, $C_{39}H_{46}O_{13}.2H_2O$, has been obtained. The sugar component has not been determined, and the aglucone has been obtained only in the amorphous form (Chen).

As mentioned earlier, in addition to the active principles possessing the characteristic cardiac effects and which are obtained from various plants, there are also the toad-venoms obtained from the secretions of certain glands of these animals. In the case of *Bufo agua*, Abel and his co-workers obtained a non-nitrogenous crystalline principle, **bufagin**. From *Bufo vulgaris*, Wieland and his collaborators obtained **bufotalin**, which was related to bufagin and a more complex non-glycosidal substance, **bufotoxin**, which consists of bufotalin in combination with arginine and suberic acid. More recently Chen, Jensen and Chen have studied the poisonous secretions of a large number of toads and have demonstrated in the secretion of the parotid glands and also in the skins the presence of bodies having a digitalis-like action.

The close relationship of the various glycosides of the digitalis series to each other is especially well shown when the aglucones into which they are hydrolyzed are arranged in a series, as follows:

Strophanthidin	$C_{23}H_{32}O_6$	Digoxigenin	$C_{23}H_{34}O_5$
Digitoxigenin	$C_{22}H_{34}O_4$	Periplogenin	$C_{23}H_{34}O_5$
Gitoxigenin	$C_{23}H_{34}O_5$	Ouabagenin	$C_{23}H_{34}O_8$

Action.—It is evident from the diversity of their chemical structure that the various digitalis-like bodies should differ to some extent in their pharmacological and therapeutic effects. Unfortunately our knowledge of these differences is still incomplete, most of our knowledge being based on a study of extracts of digitalis purpurea.

Because of its importance in therapeutics the effect of digitalis on the heart as well as on other organs and tissues has been studied exhaustively. Most of these studies have been made either on isolated preparations of the perfused heart or on animals with the heart exposed in the opened chest. Unfortunately the conclusions drawn from such observations, although accurate, are not transferable in many cases to the problem

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of therapeutics in man. As a matter of fact, much of the confusion regarding the mechanism of action of digitalis in cardiac disease of man is a result of the misapplication of data obtained by the use of large doses of digitalis in experimental preparations which are not analogous in their effects to the therapeutic doses used in the human.

Another source of confusion has arisen from the fact that the effect of digitalis on the functional activity of the heart is different in the normal from what it is under pathological conditions. Hence, observations based on a normal heart are not applicable to the diseased organ.

The **local effects** of digitalis consist in primary irritation, followed frequently by paralysis, of the sensory nerve-endings. Thus in the eye a small quantity of a solution or a minute particle of the dry poison causes the most intense pain, redness, and congestion of the conjunctiva and all the symptoms of acute inflammation. On the tongue the bitter taste is frequently followed by burning pain, and if the powder be drawn into the nostrils and larynx, marked swelling of the mucous membrane, sneezing, coughing, and hoarseness are produced in many persons. They have little action on the skin, although here too smarting is occasionally produced; but when injected subcutaneously many of them cause marked inflammation, which not infrequently ends in the formation of abscesses, even though the injection has been absolutely aseptic. This irritant action is not equally marked throughout the series, however, for digitoxin is much the most powerful in this respect, while digitalin may be injected subcutaneously without danger and almost without pain. The local anesthetic property is likewise not equally developed in all the members of the series; several of them have been suggested as local anesthetics for the eye, but their primary irritant effect precludes their use for this purpose.

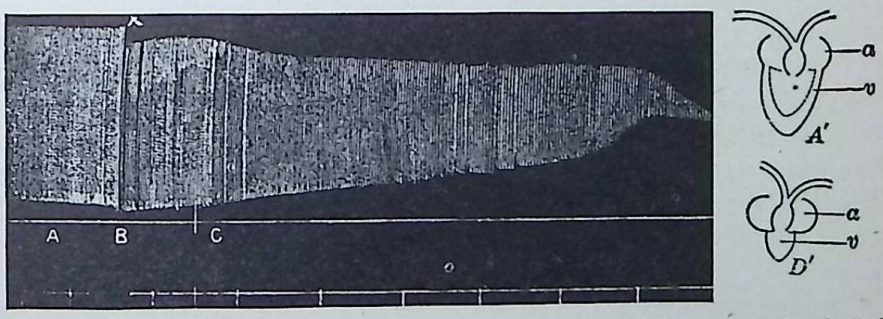

FIG. 54.—Tracing of the movements of the frog's ventricle under one of the digitalis series. *A*, normal; *B*, digitalis applied; *C*, half rhythm begins, and the diastole rapidly becomes less complete until the ventricle ceases in a position of semicontraction. *A'*, diagram of the heart in normal condition; *a*, auricle; *v*, ventricle; the dotted line represents the outline in full systole; the continuous, the outline in diastole. *D'*, outline of the heart in standstill after digitalis: the ventricle, *v*, is fully contracted, while the auricles are dilated. (After Sluytermann.)

After absorption the chief symptoms are due to their action on the central nervous system and the heart. The action on the **Central Nervous System** consists in stimulation of some of the nerve centers, which is independent of the action on the heart and is limited to the *medulla oblongata* in many cases. In the frog the excitability of the

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reflexes is often lowered by members of this series, probably because of the intense stimulation of the *medulla oblongata;* but sometimes a distinctly increased irritability is observed. More marked symptoms are produced in mammals, however, by this central nervous stimulation, for in these, vomiting is elicited very soon after the injection of large quantities long before the heart is very seriously affected, and this is due to a direct or reflex action on the central nervous system, for it is elicited in the eviscerated preparation. To the same cause is to be attributed the rapid, deep respiratory movements and convulsions, which are often observed in the later stages of poisoning and which are evidently not due to cerebral anemia, as has been supposed, for the brain at this stage receives quite as much or more blood than it normally does. Even small quantities excite the inhibitory cardiac center in the medulla and slow the heart, at least in experiments on mammals. The extent to which the members of this series act as stimulants to the nervous centers varies, but as yet little comparative work has been done in this direction.

The action on the **Heart** is the most important of all and is what distinguishes digitalis and its allies from all other substances. This action has been studied most carefully in the frog, and is here found to consist of changes in the generation and conduction of impulses and in the contractility. The power of conducting impulses is distinctly reduced, and this makes itself evident in the frequent failure of an impulse to pass from the auricle to the ventricle, which thus remains at rest during a full cycle; very often each alternate impulse of the auricle thus fails to reach the ventricle, giving rise to half rhythm; or the ventricle may remain in diastole during a series of auricular contractions, or may cease altogether in this position if very small quantities have been injected. This depressant action on conduction is accompanied by a less marked reduction of the rate of the auricle and sinus arising from fewer impulses being emitted by the pacemaker.

Along with this depression of conduction, there is a progressive increase in the strength of contraction of both auricle and ventricle. Soon the relaxation becomes imperfect, and the output falls accordingly; though the ventricle continues to empty itself more completely, it no longer contains as much blood at the beginning of systole as before. Later the apex of the ventricle remains contracted during the diastole and remains motionless and white, and this state of contraction slowly spreads over the rest of the chamber until the ventricle receives no more blood from the auricular systole, and the auricles, unable to empty themselves, come to a standstill in the dilated position.

As a general rule both these actions may be observed intermingled in the frog's heart under digitalis; the effects of the depressed conductivity generally precede those of the changed contractility and are elicited especially by very small doses. Thus when the minimal lethal dose is given, the ventricle is very often found in diastolic standstill from its failure to receive impulses from the auricle; but if it is now stimulated mechanically or electrically, it passes into complete and permanent systole. When larger quantities are given, the effects on contractility

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are elicited in greater measure, and there may be little tendency to ventricular intermission until the chamber is in almost complete systolic arrest.

The excitability of the frog's heart muscle is augmented by digitalis; thus if salt solution is led through the excised heart for some time, it ceases to beat, but if digitalis is now added to the perfusing solution, rhythmical contractions often return. This increased excitability may account for a temporary acceleration of the heart rate which is sometimes seen in the frog under digitalis.

The action on the frog's heart is a direct one on the muscle; the inhibitory mechanism has nothing to do with the change in the conduction or with that in the contractility, for the application of atropine has no effect upon either feature. The muscle of the frog's heart is thus reduced in conductivity and augmented in contractility and excitability by members of this series; the effect of the conductivity is elicited by smaller quantities than are necessary to change the contractility.

Mammalian Heart.—In the mammalian heart digitalis and its allies also affect the muscle directly, but this is complicated by inhibitory action which is absent in the frog. The direct action on the heart muscle in the healthy mammal is shown in increased strength of contraction and greater excitability, while there is less evidence of the depressed conduction which has been described in the frog's heart. Symptoms of reduced conduction occur in the mammal, it is true, but here they arise for the most part from inhibitory stimulation and not from direct muscular effects.

The action of digitalis on the healthy mammalian heart may be divided into three stages, of which the first and third are always developed when sufficient quantities are administered. The second stage may be absent in certain circumstances, but is also generally present in poisoning.

In the *first or therapeutic stage* of the action of this series (Fig. 55), the rhythm of the heart is distinctly slower than before the drug, for the inhibitory apparatus is set in activity, and the slowing is accordingly due to a prolongation of the pause in diastole. The ventricles contract to a smaller size; that is, they empty themselves more completely than they normally do. This increased contraction is, like that in the frog's heart, due to action on the cardiac muscle. The papillary muscles undergo the same changes as the rest of the ventricular wall, contracting more strongly and more completely than before the administration of the drug.

The relaxation of the ventricle is found to vary in different conditions. If the heart is weak and dilated, digitalis and its allies tend to lessen this dilatation; that is, the relaxation of the ventricle during diastole is less than before the administration of the drug. If, however, the heart is normal, or does not dilate much during diastole, digitalis increases the relaxation (Fig. 55). The variation in the degree of dilatation of the ventricle depends upon the opposing factors—the inhibition and the muscular action. If the inhibition be the stronger, the ventricle relaxes more completely than before, for vagus stimulation always

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tends to increase the relaxation of the heart. If, on the other hand, the muscular action predominates, the relaxation is lessened, for here, as in the frog's heart, this series tends to lessen the extent of relaxation. In the normal heart the application of one of this series causes, as a general rule, an increase in the extent of relaxation.

It must be added that the inhibition is due to the stimulation of the vagus center in the medulla only; the peripheral mechanism is little involved, for digitalis hardly slows the heart after section of the vagi, as it would do if it acted on the intracardiac inhibitory ganglia or nerve ends.

Each beat of the ventricle thus expels more blood under digitalis than before, and if the number of beats per minute remained the same, the amount of blood expelled (or the output) would be much increased; but the rhythm is slower than normal, and this may more than compensate for the larger amount of blood expelled by each individual beat. In the therapeutic stage the slowing is not great enough to counterbalance the increased output per beat, and a larger amount of blood is therefore driven into the aorta and pulmonary artery.

The changes in the ventricle, then, are due to inhibitory activity and to direct cardiac action, the first tending to lessen the number of beats and to increase the relaxation of the fibers, the second tending to strengthen the systole and to limit the relaxation while not affecting the rhythm.

In the auricles the inhibitory stimulation causes more or less increase in the dilatation, while it lessens the contraction. The muscular action is the same here as in the ventricle, causing a tendency toward more complete systole and less complete relaxation. After small quantities, the rhythm of the auricle is slow, like that of the ventricle, owing to the inhibition; the relaxation is little changed, but, owing to the muscular action, the contraction is more complete. In but slightly larger quantities, however, the inhibitory action causes a less complete contraction, so that the work done by the auricle is actually less than before the injection.

The rhythm of the different parts of the heart is exactly the same during this stage, and the changes seen in the right auricle and ventricle correspond to those in the left. The conduction of impulses from the auricle to the ventricle may be slower owing to the connecting fibers being depressed by the inhibitory activity.

In the *second stage* of digitalis action (Fig. 55, *C*) the symptoms are due to excessive inhibitory activity, while the direct cardiac action is less developed. The rhythm of the ventricle, and consequently of the pulse, is very slow and irregular, as is always the case when the inhibitory apparatus is strongly stimulated. During diastole the ventricle dilates more completely than usual, while its systole continues powerful, since the inhibitory stimulation increases the relaxation but has less power to diminish the contraction. Each beat expels more blood than normally, but the rhythm is so slow that the output per minute and the efficiency of the heart as a pump are less than usual. This is the feature which differentiates the first from the second stage,

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in which the same factors are present; in the first stage the efficiency of the heart, *i. e.*, the amount of blood expelled per minute, is greater; in the second stage it is less than before the administration of the drug.

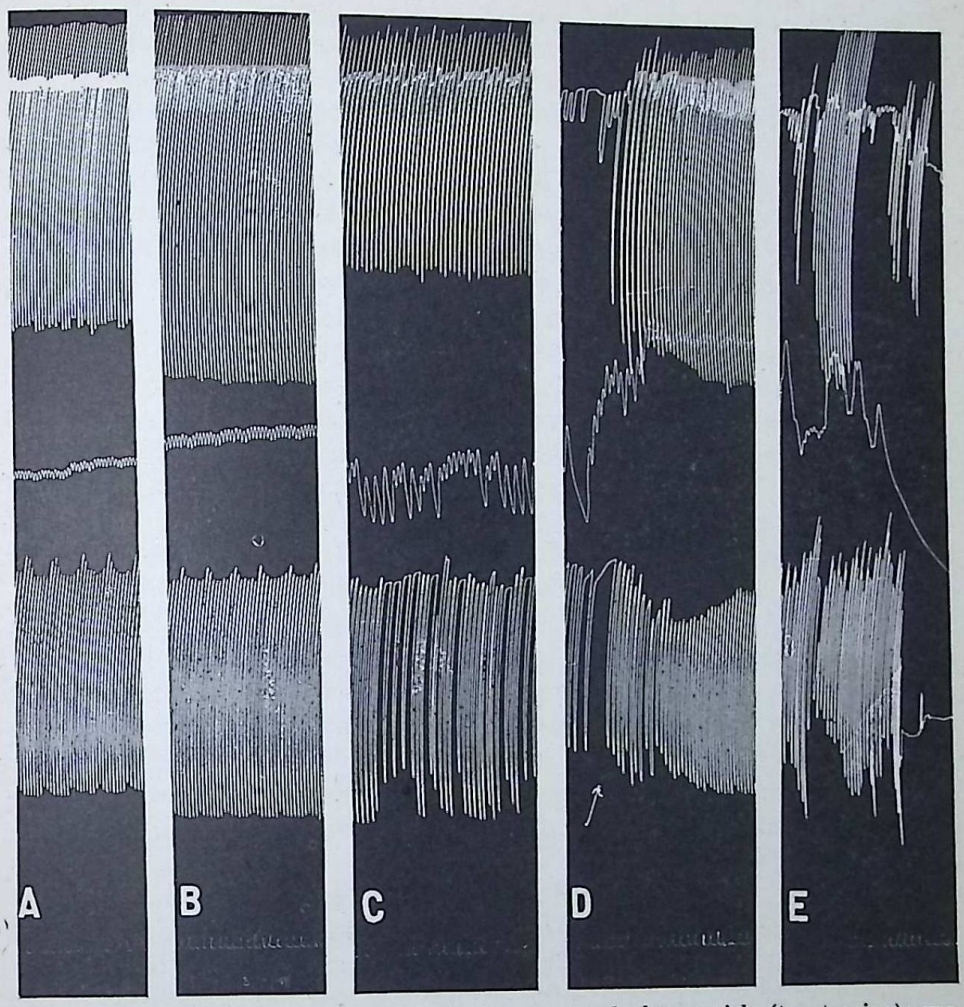

FIG. 55.—Digitalis on the dog's heart. Levers attached to auricle (top tracing); ventricle (lower tracing); middle tracing is blood-pressure. Myocardial levers move down in systole. Time in seconds. *A*, Normal tracing. *B*, Small dose of digitalis giving increase in systole of both chambers and some rise in blood-pressure (therapeutic stage). *C*, Toxic dose. Marked slowing with partial heart block; irregular pulse with low blood-pressure. *D*, Vagi cut with removal of slowing; high (toxic) blood-pressure. *E*, Final toxic stage with great irregularity—both chambers finally passing into delirium with fall of blood-pressure to zero.

Very often the impulses have difficulty in passing from the auricle to the ventricle (heart-block) owing to the inhibition of the conducting fibers. The ventricle then beats at a slower rate than the auricle, but if the irritability of the ventricle is increased at the same time as the conduction falls, there may arise a spontaneous rhythm in the ventricle, which is independent of, and different from, that in the auricle.

The auricular contractions are much weaker than in the first stage, and even than in the normal heart, and may cease altogether for some time, while the chambers do not tend to dilate further as a general rule.

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This stage of excessive inhibition is not observed in every case of poisoning in animals, nor probably in man, although in the recorded instances of poisoning with the members of this series, it seems to have been present, as the pulse is said to have been very slow and irregular. If the inhibitory mechanism is weak, or is paralyzed by the preliminary injection of such drugs as atropine, the second stage is entirely absent.

When still larger quantities of any of this series are injected, the *third stage* may set in. It is preceded by the first for a short time, generally by both first and second. In this stage the ventricular rhythm becomes very much accelerated, usually much beyond the normal, and even beyond that seen after paralysis of the inhibitory nerves. This acceleration is not produced by paralysis of the vagus, for stimulation of this nerve sometimes still slows the heart and always causes dilatation. It is really due to the drug increasing the irritability of the heart muscle to such an extent that the inhibitory apparatus is no longer able to hold it in check.

The auricles also undergo the same changes. They begin to accelerate their rhythm, which may diverge from that of the ventricle, and the difference in rhythm of the two divisions may lead to a very characteristic periodic variation in the strength of the contractions of both auricle and ventricle. This auriculo-ventricular arrhythmia may continue for some time, but further irregularities soon present themselves. At intervals, extrasystoles of either ventricle or auricle appear; that is, two contractions follow so rapidly on each other that the chamber has no time to dilate fully between them and no blood is expelled by the second one. These extrasystoles become more numerous, and soon form groups of two or three, separated by other groups of ordinary contractions. The rhythm becomes more rapid and more irregular and this culminates finally in fibrillation of the auricle and ventricle (Fig. 55, *E*, p. 621).

All the features of the third stage are due to the poison increasing the spontaneous excitability of the heart muscle. This increased excitability in the pacemaker leads to acceleration of the beat of the whole heart, but larger amounts arouse the normally dormant areas in the A–V node and in the ventricle, and lead to impulses being discharged from them and causing contractions of abnormal origin and irregular rhythm. In the ventricle this increased excitability leads to the development of a rapid spontaneous rhythm, extrasystoles, and finally fibrillation. In the third stage the conduction from auricle to ventricle is reduced or completely destroyed, and this change differs from the impairment of the conduction seen in the earlier stages in being due to the direct action on the muscle and not to the inhibitory mechanism. In fact, in the third stage the latter is not an important factor, the increased excitability and decreased conduction both arising from the direct heart action.

Throughout the whole course of the intoxication the two ventricles beat in unison, and the two auricles also maintain the same rhythm throughout, but the rhythm of the ventricles may, as has been stated,

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be entirely different from that of the auricles in either the second or third stage.

Almost all the features observed in the frog's heart under digitalis may also be found in the mammal, and in addition the latter shows the effects of inhibitory stimulation which are not seen in the frog. The inhibition is the cause of the slow rhythm and block in the earlier phases of digitalis action in the healthy mammalian heart, and the direct action on the conducting fibers can be made out only in the late stages of poisoning; in the frog, on the other hand, the slowing and block arise from the direct action only. In the mammalian heart in extreme malnutrition the reaction resembles that in the frog; the rhythm is slowed and the conduction is impaired through direct action on the cardiac muscle, for it is not prevented by atropine, which excludes all inhibitory activity.

Cattell and Gold demonstrated, by means of the isolated papillary muscle of the cat undergoing stimulation at a uniform rate, that digitalis exerts a direct action upon cardiac muscle, increasing the force of its contractions. This change, being produced in the isolated muscle where coronary circulatory changes and alterations in heart rate are absent, shows that these latter factors are not necessary to account for the beneficial effects of the drug upon the action of the heart.

Büchner has shown that in cats the administration of large doses of the digitalis group of glycosides is followed by definite pathological changes in the cardiac muscle, which may lead to death in a few days, or in the event that a second dose of digitalis is given it may lead to death, even though the amount administered is merely a fraction of the normal lethal dose (Bauer).

Vessels.—Small quantities of digitalis and its allies, such as are used in medicine, have no direct action on the blood-vessels, but larger amounts induce changes in the muscular coat which present some analogy to the changes in the heart muscle. The latter, however, is much more sensitive to the glycosides than the arterial walls, and an amount of digitalis which is capable of acting on the vessels proves fatal to the heart in the course of a few minutes. The vascular action has thus no therapeutic importance. It may be observed by perfusing the surviving vessels with digitalis in Ringer's solution in the frog or mammal. The glycosides vary considerably in their power of contracting the vessels when thus perfused, as digitoxin is distinctly more powerful than strophanthin in contracting them. The different vessels also vary in their reaction, those of the intestinal area contracting more readily than those of the kidney, which again appear less susceptible than those of the limbs and brain; the coronary arteries of the heart appear to resemble those of the limbs in contracting when digitoxin is perfused through them, while strophanthin has less effect on their caliber; but therapeutic doses probably have no direct action on the coronaries.

The Blood-pressure.—The changes in the heart and vessels are reflected in the blood-pressure, and it is possible that an additional factor may be involved in the action of some of the glycosides on the vasomotor center.

In man therapeutic doses of digitalis do not cause any very appreciable change in blood-pressure. In a certain number of cases the systolic pressure is raised; in others it may be lowered, but in the majority of

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cases no change takes place. The drug, in general, tends to bring the systolic pressure back toward the normal. The action on the diastolic pressure is more uniform, as in the majority of instances it is reduced, the net result being to increase materially the pulse-pressure. In patients suffering from heart failure there may be an increased pressure associated with cyanosis, dyspnea, and circulatory stasis, and the administration of drugs of this group is often followed by improvement in the clinical symptoms and a distinct lowering in blood-pressure. In such cases of heart failure the vasomotor center is in a state of unusual activity because the circulation is deficient, with resulting poor oxygenation of the blood and cyanosis. As digitalis strengthens the heart, thereby improving the circulation of the blood, the vasomotor center lessens its activity, the vessels relax, and the blood-pressure may be lowered.

In animals quantities of digitalis which are sufficient to affect the heart do not increase the blood-pressure appreciably. The increased efficiency of the heart in itself in the first stage would increase the arterial tension, but this appears to be compensated by a slight diminution in the tone of the vasomotor center, which reduces the resistance in the peripheral vessels and thus permits a freer passage to the blood. In other words, an augmented efficiency of the heart must lead to a rise in blood-pressure if the vessels remain unchanged in caliber but may lead to an accelerated flow through the tissues if the vessels relax in proportion as the output of the heart increases. Such an acceleration of the circulation has been observed repeatedly under small quantities of digitalis in animals.

As long as this compensatory action persists in the vasomotor center, the blood-pressure does not rise from the cardiac action; in man this balance between the heart and the vasomotor center is more perfect than in the lower mammals, and in man changes in the blood-pressure are thus more carefully guarded against, and no alteration is usually caused by therapeutic doses of digitalis which increase the cardiac output.

In experiments in animals a rise in blood-pressure is generally observed under the members of this group (Fig. 55, p. 621), partly because in the lower mammals the balance between the activity of the heart and the vasomotor center is less developed than in man and in addition is rendered less active by the anesthesia, but mainly because much larger quantities are injected in order to induce a rapid effect, such as can be observed in the course of an hour. These larger doses introduce a new factor, however, in the direct action on the vessel walls, which precludes the compensatory activity of the vasomotor center, and thus the blood-pressure rises, partly from the increased efficiency of the heart and partly from the unusual resistance to the passage of the blood out of the arteries.

Action on the Renal Secretion.—When digitalis was first introduced to the notice of the medical profession by Withering, its action on the heart was not appreciated. Withering used it only to remove accumulations of fluid from the body, which it accomplished by increasing the secretion of urine. This observation of Withering was soon confirmed by further experience in the use of this drug, but it was long disputed whether this diuretic action occurred in health, or whether it

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was not confined to cases in which pathological accumulations of fluid were present. Digitalis, however, as is now conceded by almost everyone, causes some increase in the quantity of urine secreted by the normal animal, although this is small compared with that in cases of dropsy. The fluid of the urine is more largely augmented than the solids, though the chlorides and uric acid are both increased in the urine and as a consequence decreased in the blood. The increase in the urine arises not from a direct action on the kidney, such as is met with under caffeine, but only indirectly through the changes in the circulation; the kidney shares in the general improvement in the circulation and functions more vigorously. At the same time the general circulatory changes promote the interchange of blood and lymph, and any accumulation of fluid in the body tends to be reabsorbed into the blood-vessels and then to be got rid of through the kidneys. The diuretic action of digitalis is therefore secondary to the improved blood flow and is a result of the changes in the heart alone.

Scillaren, the crystalline glycoside derived from Squill, is believed to exert a direct action on the renal epithelium. This, in addition to its action on the heart, renders it a more effective diuretic than the cardiotonics derived from the digitalis bodies (Stoll).

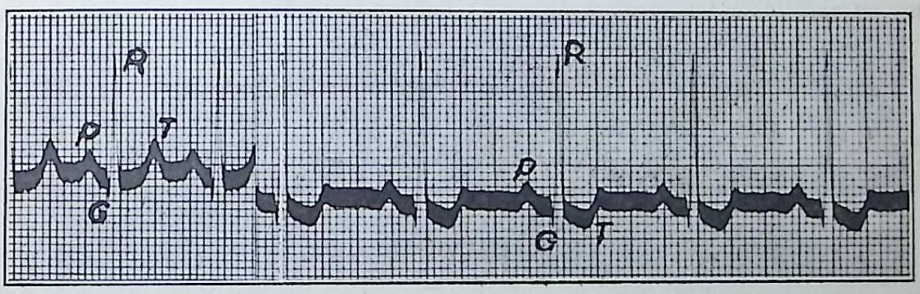

FIG. 56.—Electrocardiograms (Lead II) taken from the same patient before and after digitalis had been given. The first curve is a normal electrocardiogram with a heart rate of 94 per minute and a *P–R* interval of 0.16 second. The second curve shows characteristic digitalis inversion of the *T*-waves. The ventricular rate is 77 per minute and the *P–R* interval is at the upper limit of normal, measuring 0.2 second. The increase in the *P–R* interval is probably due to digitalis. Time lines represent fifths and twenty-fifths of a second.

The Changes in the Circulation in Man have been followed only imperfectly, owing to the manifest difficulties of estimating the strength and efficiency of the heart contractions. Recently the action of digitalis upon the extent of contraction of the human heart has been definitely shown by means of moving roentgen-ray pictures and by studies on the cardiac output. In patients with auricular fibrillation as well as in those with a normal rhythm a distinct increase in the extent of the left ventricular excursion was shown. In many cases no definite alteration in the rhythm follows digitalis treatment even when it is pushed until nausea and vomiting occur. In others, the pulse is distinctly slower, stronger, and fuller than before the administration of the drug. It must be added that the strength of the pulse is not to be regarded as a gauge of the changes in the cardiac muscle, for it is due not only to the

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increased strength of the cardiac contraction, but also to the slow rhythm. When the heart is beating rapidly, the arteries have no time to empty themselves completely, and the pulse is small, while on the other hand, when digitalis slows the heart, the arteries have time to empty their contents into the capillaries before the next contraction occurs, the walls therefore become more flaccid, and a new wave of blood causes a more distinct impulse. In some cases the pulse remains unchanged in rate, but there may be other evidences of the action of the drug, such as an increase in the secretion.

Electrocardiographic records also show that in most cases the pause between the auricular and ventricular contractions is lengthened, indicating that the conduction is impaired (Fig. 56).

In all subjects, normal as well as those suffering from heart failure, alterations in form of the T waves of the electrocardiogram follow the administration of digitalis. They are frequently the earliest effects observed. The most characteristic and usual effect is negativity of T_3, but in certain cases T_1 and T_2 also become negative. The T wave in all three leads sometimes becomes diphasic. Waves which are negative prior to administration of digitalis may become positive, or the amplitude only of the waves may be changed. The injection of atropine does not modify this digitalis phenomenon, demonstrating that it is due to an action of digitalis upon the heart muscle.

This change in the electrocardiogram is of considerable importance as it is perhaps the earliest sign that digitalis is acting upon the heart, appearing as it does before nausea and vomiting disturb the patient or even before changes in rhythm or alterations in conduction time have occurred.

In a series of very carefully controlled investigations Stewart and Cohn have shown that in **normal individuals** an effective dose of digitalis decreases the output of blood from the heart and at the same time decreases the size of the heart. Changes in the T-wave curve were apparent in two and a half hours after the drug had been taken by mouth, while the output and area changes began to appear in four hours, reaching their maximum within twenty-four hours. Changes in arterial or venous pressure were not marked. Following the maximum effects of the drug, gradual recovery took place, but the duration of action varied widely in different individuals, in some cases return to normal being a matter of a few days, while in others normal output and cardiac area were not restored for weeks.

During this period, when the cardiac output is from 65 to 80 per cent of normal, the patient is often conscious that the heart is beating forcefully, and there is dyspnea on exertion and some cardiac pain, probably due to anoxemia of the cardiac muscle from interference with the coronary blood flow.

In patients with **cardiac failure**, either when the cardiac mechanism is normal or when auricular fibrillation is present, the cardiac output is low and, as is well known, the cardiac area is increased and the venous pressure is high. In such cases adequate doses of digitalis will increase

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the output, lessen the cardiac area, and lower the venous pressure. Slowing of the ventricular rate also occurs.

The great point of difference between the effect of digitalis in the normal individual and the one with cardiac failure is that in the former the cardiac output is markedly lessened by digitalis while in the cardiac case it may be greatly increased, the area in either case being decreased. The explanation of this apparent contradiction is doubtless to be found in the fact that under normal conditions the heart size is probably at an optimum for the performance of its work as a pump. Digitalis decreases its size, as shown by a change in the surface area to three-quarters or four-fifths normal, and to that extent lessens its efficiency and therefore its output.

In the enlarged heart of **decompensation**, however, the cavities are dilated, the contractile power in the wall of the heart is inadequate and the output is correspondingly low. Under digitalis the size of the cavities is lessened, but not to a degree less than normal, and in this state they are able to eject larger quantities of blood. By increasing the tone of the cardiac muscle, the size of the cavities is decreased and the heart is more effectively emptied. In addition, the stimulating effect of digitalis on the force of contraction further increases the output per beat. Even with a decrease in pulse rate, the effect of digitalis is to increase the total output per minute of the dilated heart.

The action of strophanthus and of other purified digitalis bodies injected intravenously has been shown to be essentially like that of digitalis except that the action is much more rapid than it is with digitalis given by mouth. In some cases of severe decompensation, a few minutes only were sufficient to increase markedly the cardiac output and the systolic output (Fraenkel).

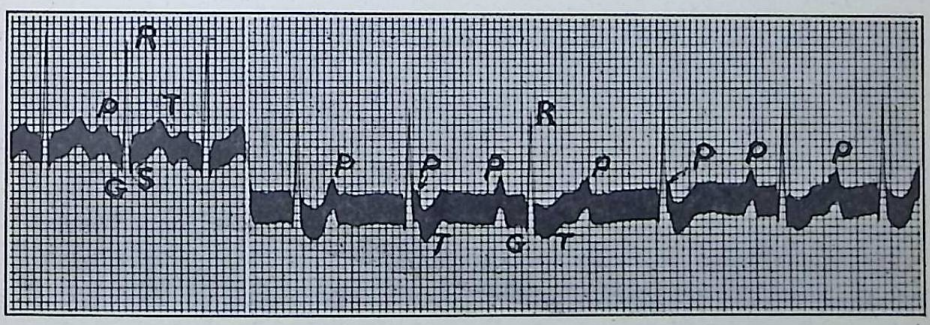

FIG. 57.—Electrocardiograms (Lead II). These tracings are both taken from a boy with rheumatic heart disease. The first curve is not abnormal except for a sinus tachycardia, the heart rate being 136 per minute. The second curve shows the effects of over-digitalization. Partial *A–V* heart block with frequent dropped beats and ventricular escapes is seen, and the *T*-waves show marked inversion. Time lines represent fifths and twenty-fifths of a second.

The use of digitalis sometimes gives rise to irregularities, and the character of these has received a good deal of attention of late years. The first form arises from the muscular action, which may increase the excitability of the ventricle or auricle so much that spontaneous beats (extrasystoles) arise. When these occur, the heart should be carefully

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watched, and the dose should be reduced (Fig. 57). To what extent other forms of arrhythmia arise from the stimulation of the inhibitory mechanism by vagus stimulation is questionable, although this mechanism was formerly believed to play an important rôle in the slowing of the heart by digitalis in therapeutic doses. The slowing which occurs in normal people in correspondence with the breathing (sinus arrhythmia) may be exaggerated, and the slow, powerful contractions cause an unpleasant sensation in the chest. This occurs when the vagus is

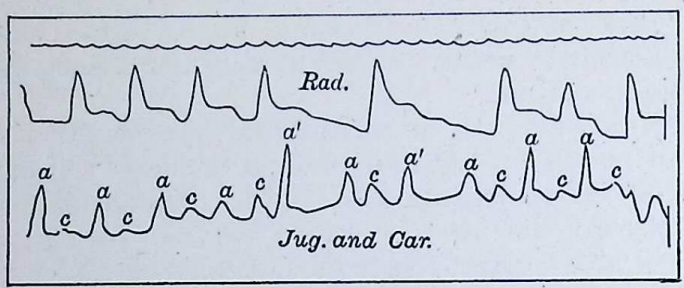

FIG. 58.—Tracings from the radial artery and the jugular vein in a case of heart disease treated with digitalis in large doses. The waves *a*, *a'* on the jugular tracing indicate the auricular contractions and are seen to be perfectly regular in rhythm throughout; the auricle is, therefore, beating regularly. The radial pulse intermits at intervals, showing that the ventricle has not responded to the impulses which in the auricle gave rise to the contractions indicated by *a'*. (Mackenzie.)

strongly stimulated from any cause and is not peculiar to digitalis. When this form of irregularity sets in, the dose should be reduced or the drug omitted altogether for a few days. Not infrequently, a less obvious vagus effect causes irregularity under digitalis; the passage of impulses from the auricle to the ventricle is retarded or entirely arrested, from the conduction through the connecting fibers being reduced.

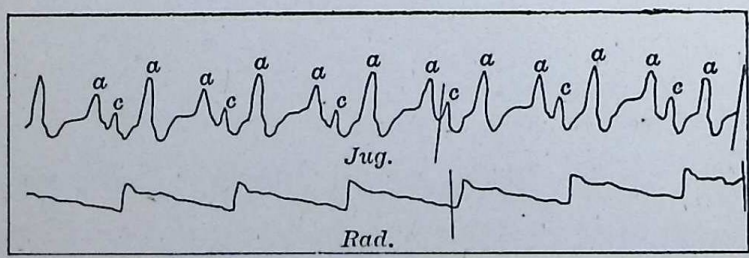

FIG. 59.—Slowing of the pulse due to digitalis depressing conductivity, so that the ventricle fails to respond to every second stimulus from the auricle. While the ventricle contracted forty-eight times per minute, the auricle contracted ninety-six times. (Mackenzie.)

Before the treatment the fibers were able to conduct all the impulses from the auricle to the ventricle. But now an occasional impulse fails to pass, or perhaps only one of two impulses passes to the ventricle. When an impulse fails to reach it, the ventricle remains in diastole (dropped beat) (Fig. 58), and when only one-half of the impulses pass to it, the rhythm of the ventricle is only half that of the auricle (half-rhythm) (Fig. 59). Or the block may be complete, no impulses passing through the fibers at all, and in this case the ventricle takes up its own

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spontaneous rhythm (heart-block) (Fig. 60). Another form of block may occur between the sinus and the auricle (sino-auricular block), and both auricle and ventricle now intermit a contraction at variable intervals. In all these forms digitalis interferes with the passage of impulses from the auricle to the ventricle, or from the sinus to the auricle, by stimulating the inhibitory mechanism, which lessens the conductivity of the connecting fibers. The irregularity therefore disappears under atropine, which paralyzes the inhibitory mechanism. In rarer cases, however, the digitalis heart-block does not arise from the inhibitory stimulation but from direct action on the conducting fibers, and this form of block, which may be sino-auricular or auriculo-ventricular, is not relieved by atropine. The inhibitory block under digitalis is similar to that seen in experiments on mammals in the second stage, while the rarer block from direct action is the same as that seen in the frog, in the ill-nourished mammalian heart, and in the human heart in auricular fibrillation.

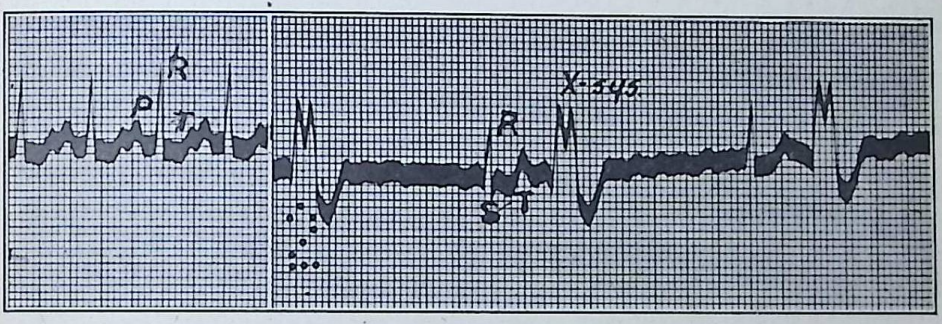

FIG. 60.—Electrocardiograms (Lead II). The first curve was taken from a patient with resolving pneumonia and shows sinus tachycardia, with a rate of approximately 135 per minute, and partial inversion of the *T*-waves. Because of the tachycardia the *P* and *T*-deflections are partially superimposed. The second curve was taken from the same patient after auricular fibrillation had developed and too much digitalis had been given. The ventricular rate is very slow and nearly regular, suggesting complete *A–V* dissociation. Each ventricular beat is followed by a ventricular extrasystole, causing bigeminy. Time lines represent fifths and twenty-fifths of a second.

Mechanism of Action.—The mechanism by which digitalis exerts its beneficent therapeutic effects in abolishing heart failure has been the subject of much argument. The favorable response has been attributed to the slowing of the heart rate, to an increase in cardiac tone, that is, reducing the diastolic size so as to allow a more effective emptying, pooling of blood in the veins by constriction of hepatic veins, and to direct stimulation of the myocardial muscle, causing it to contract more efficiently.

The fact that a favorable response is also obtained in patients who do not manifest a slowing of the heart is evidence that this factor cannot play a decisive rôle. In fact, it is very probable that the slowing of the heart following the use of digitalis is secondary to its improved function rather than the cause of the improvement.

The most important factor involved in the improvement which follows the use of digitalis is the direct stimulating effect of this drug on

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the force of contraction of the heart. Not only does the heart contract more effectively but it also utilizes its energy more efficiently (Peters and Visscher). This is aided no doubt by the increased tone which the heart manifests under the influence of digitalis, thereby overcoming the effects of overdistention which interfere with effective contraction.

In the doses used in therapeutics it is unlikely that digitalis affects the caliber of the vessels and, hence, that any assumed effect on the hepatic veins plays a part in abolishing heart failure.

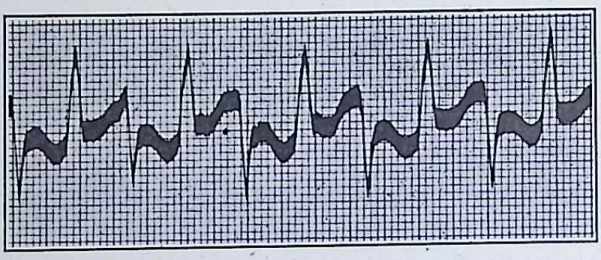

FIG. 61.—Electrocardiogram (Lead II) taken from a patient having auricular fibrillation and high grade digitalis intoxication. The curve shows a ventricular tachycardia with a rate of 168 per minute. The alternation in the type of complexes indicates that the ventricular beats are arising alternately from two different foci in the ventricles. The prognosis is very bad when this type of tachycardia appears. Time lines represent fifths and twenty-fifths of a second.

In fever the **Temperature** is not infrequently reduced, although it remains unchanged after the administration of digitalis to the normal animal. This action is said by some to be the result of collapse, while others believe it to be due to the changes in the circulation, but neither of these seems to be a very happy explanation. It has been stated already that the members of this series act as stimulants to some parts of the central nervous system, and a possible explanation of their antipyretic action would be an increased activity of the temperature-controlling centers. It has been shown by Harnack that several central nervous stimulants, including picrotoxin, cause a fall in the temperature in this way. Injection of digitalis in large doses in patients with congestive failure, but without cirrhosis of the liver, results in a momentary increase in the oxygen consumption and blood-pressure, followed by a considerable reduction in both of these functions (Nylin).

Absorption and Distribution.—The glycosides of this series are peculiarly susceptible to destruction in the alimentary tract, and there is no doubt that a part of those taken by the mouth is rendered inert in the stomach and bowel. After a dose of digitalis leaves, the glycosides may be found in the stomach and upper part of the small intestine, but none reach the large bowel unchanged. In addition, the absorption is very slow from the alimentary tract for most of the members of the group, and this is especially true for strophanthus. Digitoxin and the tincture of digitalis seem to form an exception to the rule, as they are absorbed quite rapidly. It has been shown that when full therapeutic doses of the tincture are given by mouth an effect, demonstrated by a change in the T wave, will be obtained in almost all patients in from three to four hours, and a

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maximum effect in from six to seven hours, and the same is maintained for at least twenty-four hours.

Digitalis is slowly destroyed and eliminated, the rate for this destruction having been calculated to be equivalent to about 0.12 grams in twenty-four hours. This fact is of great clinical interest and importance because, after a patient has been digitalized satisfactorily, it is only necessary to give such an amount of the drug as will replace the amount destroyed or excreted. Naturally there are individual variations, as some patients destroy the drug more slowly, and others more rapidly, than the figure mentioned.

On hypodermic injection, the glycosides cause marked local irritation, and a considerable proportion also seems to undergo decomposition, for much larger quantities are required to induce changes in the heart than are necessary by intravenous injection. Some of the principles have been found in the urine and feces, so both kidney and gut share in the excretion.

Digitalis bodies may be present in the excessive body fluids of edematous patients for digitalized persons who are given also the organic mercurial diuretics with resulting active diuresis frequently display symptoms suggestive of digitalis poisoning. The mobilization of the edematous fluid in its passage to the kidneys apparently subjects the heart to sufficient additional digitalis to produce the symptoms of poisoning (Schnitker and Levine).

After they reach the blood, the action of the bodies of this series is very prolonged, the heart only regaining its ordinary rate several days after the drug has been stopped. If the dose be repeated, the action therefore becomes more and more marked (cumulative action) as the glycoside increases in concentration, and a dose which improves the condition at first may, if continued, lead to poisoning. The different glycosides differ in the duration of their action; thus Hatcher estimates that seven-eighths of the strophanthin in the tissues is eliminated within twenty-four hours, while one-half the principles of digitalis remain active after four days.

Tolerance.—Some species of animals tolerate much larger quantities of the digitalis bodies than others. For example, the snake and toad are not poisoned by amounts which would be fatal to the frog. This arises from the tissues of these tolerant animals not being susceptible to the poisons, and not from any difficulty in absorption or rapidity of excretion; for the isolated hearts in these animals show the same refractory behavior as the intact animal. Among the mammals, the rat's heart has been shown to be much less susceptible to the action of these bodies than the rabbit's. Tolerance has not been shown to be acquired for digitalis and its allies through their prolonged use.

Therapeutic Uses.—Digitalis has long been the sheet anchor in treatment of diseases of the heart, but little was done to elucidate its clinical action until the early part of this century. Much still remains to be investigated, but it has at least been determined that it is much more efficacious in certain forms of cardiac impairment than in others. Its most remarkable therapeutic effects are seen in cases of **rheumatic heart**

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disease with auricular fibrillation. In this condition the auricular muscle is the seat of so-called circus contractions which keep that chamber in continuous incoördinate activity which prevents its emptying its contents into the ventricle. The multitudinous impulses generated in the auricles descend irregularly to the ventricle, which responds with a rapid beat varying not only in rhythm but also in strength; many of the contractions are too weak to expel any blood into the aorta, while others cause large pulses, and these are intermixed in the most confused fashion; the pulse is thus extremely irregular (Fig. 62). This irregular heart is quite compatible with moderate health for long periods, but sooner or later the signs of failing circulation appear, the pulse becomes alarmingly rapid, and congestive failure develops quickly. If digitalis is now exhibited in full doses, these symptoms of heart failure abate rapidly, improvement beginning after six to twenty-four hours, according to the method of administration. If strophanthin (0.5 mg.) is injected intravenously, the improvement begins within two hours and is marked in eight to twelve hours. In each case the pulse rate falls, and this slowing

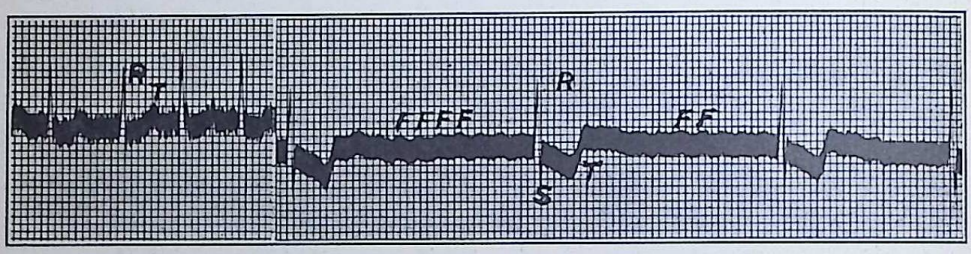

FIG. 62.—Electrocardiogram (Lead II). Both of these tracings are taken from a patient with auricular fibrillation. The first curve taken before digitalis therapy was started shows rapid irregular ventricular responses with an average rate of 165 per minute. The *T*-waves are upright. The second curve taken after the patient was completely digitalized shows the slow regular ventricular responses at an average rate of 56 per minute and marked *T*-wave inversion. The fibrillation waves (marked *F*) are clearly seen. Time lines represent fifths and twenty-fifths of a second.

proceeds in proportion to the general improvement and may be taken as a measure of it. The heart may be slowed from 130 to 150 per minute to 50 to 60 in the course of a few hours, and at the same time the beats become stronger and more equal in size and in time (Fig. 62). The auricles continue to fibrillate after the pulse is slowed, but the ventricle responds to fewer of the impulses emitted by the auricle and with each contraction ejects more blood into the arterial system.

The slowing of the pulse in auricular fibrillation does not arise from inhibitory action alone, for it is not entirely prevented by atropine; in fact, when a patient is under digitalis and the pulse is slowed, the inhibitory mechanism is less active than before treatment when the pulse was rapid; this is shown by the fact that paralysis of the inhibition by atropine does not accelerate the heart so much under digitalis in these cases as it did before treatment was begun. In digitalized patients with auricular fibrillation, the ventricle is slowed as a result both of inhibition of the vagal center, as well as by an extravagal factor, not abolished by atropine. The degree of digitalization determines the relative extent to

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which each of these factors is responsible for the observed slowing (Gold *et al.*). Auricular fibrillation can be induced experimentally in animals by electrical stimulation of the auricle, and when this is done in a healthy heart digitalis does not render the ventricular beat slow and regular as it does in auricular fibrillation in man. But if this condition is induced in a perfused, badly nourished heart, digitalis slows the ventricle and makes it regular exactly as in clinical cases. The therapeutic action of digitalis in auricular fibrillation is thus due to the specific muscular action on the strength of contraction and on conduction, such as is seen in the frog and in the mammalian heart in malnutrition.

Not infrequently in this condition the dose has to be very large, and if it be continued the patient suffers from nausea and vomiting. Or the pulse may fall to from 50 to 100 per minute (Fig. 62) and become regular; the ventricle now responds no longer to impulses from the auricle but has developed its own spontaneous regular rhythm. More frequently the heart develops the bigeminus form shown in Figure 60, in which each full beat is followed very quickly by a secondary one; here the large contractions arise from auricular impulses, but the excitability of the ventricle has risen to a point at which it also discharges impulses, and this coupled rhythm is the result. These are all indications that the drug has been pushed too far, and they all disappear when the dose is reduced.

In some cases of auricular fibrillation in which the heart is not much accelerated, digitalis has no such striking effect, even though improvement occurs under it. Even when digitalis relieves the symptoms of heart failure in auricular fibrillation, it does not arrest the underlying process, and the auricle continues to beat in its previous irregular way. Digitalis prevents the ventricle from being exhausted by increasing its tone and by limiting the number of impulses which descend from the auricle. That the increase in tone and strength of contraction rather than the effect on the conduction system is responsible for the improvement in the circulation is shown by the fact that quinidine (*cf.* p. 708), which arrests the irregular beating of the auricle, does not give the improvement shown by digitalis.

Digitalis is also used in the treatment of certain cardiac arrhythmias. It is used in abolishing **auricular tachycardia** and in preventing the recurrence of the paroxysms. In **auricular flutter**, it is also effective and is used in cases which fail to respond to quinidine. In this condition the auricle is again the seat of abnormal excitation and beats at a very high rate but quite regularly. The ventricle is also regular though very rapid and responds to only half of the impulses descending from the auricle; the rapid rhythm of the ventricle tends to exhaust it and calls for treatment. Digitalis given in full doses changes the regular flutter to fibrillation and at the same time reduces the conductivity of the His bundle, so that the beat of the ventricle becomes very slow, sometimes only 30 to 40 beats a minute. Upon stopping the treatment both flutter and fibrillation are found to have ceased and the heart beats in normal rhythm. The explanation seems to be that digitalis, either

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through its vagus or its muscular action, further excites the auricle and changes the flutter to fibrillation; but fibrillation of recent development tends to revert to normal rhythm and when the digitalis action passes off, the flutter does not return, but the normal pacemaker resumes its sway.

In **other forms of heart disease** the effects of digitalis are less spectacular, and although improvement undoubtedly results from the treatment, there is no such guide as is offered by the slowing of the pulse in fibrillation. It is therefore not always easy to determine how far the improvement is to be attributed to the digitalis and how far to such auxiliaries as rest and general treatment. Such measurable symptoms as dropsy are often presented, however, and the fall in weight from diuresis under digitalis is as significant evidence as the fall in pulse rate in fibrillation. In general terms it may be said that improvement is seen in a large number of conditions in which the efficiency of the heart is impaired and the blood is no longer pumped from the venous reservoirs to the arteries in adequate amount. The deficient circulation no longer suffices to maintain the nutrition of the tissues, including the heart, and dilatation of the heart chambers, congestion of the lungs, edema and dropsy follow; the kidneys and other organs become overfilled with venous blood, and the whole economy is thrown into disorder. The treatment obviously comprises rest to relieve the strained organs, along with some member of this series to increase the strength of the contractions of the heart and thus to compensate for the disorders which are the primary cause of the condition. Under digitalis such improvement occurs; the congestion disappears; the kidneys secrete more rapidly and drain off the accumulations of fluid in the tissues and cavities of the body. The heart itself is better nourished through the acceleration of the blood stream and is now able to meet the strain thrown upon it by such damage as destruction of the valves. The only action of the drug which seems to be necessary for this purpose is its power to increase the strength of the contraction. Even in cases where the pulse rate is slow, digitalis may exert its beneficent effects by its action in strengthening the force of cardiac contraction. In the presence of complete heart block, which formerly was considered a contraindication to the use of digitalis, improvement may follow the use of digitalis in certain cases manifesting cardiac insufficiency.

The beneficial action of digitalis is generally stated to be more obvious in disease of the mitral than in that of the aortic valve. This view may have arisen from the fact that mitral disease is often accompanied by auricular fibrillation. In some cases of aortic valve failure digitalis appears to be of value, but there seems some reason to doubt whether it is as often efficacious as in mitral disease, even when the fibrillation cases are excluded.

In experimental lesions of the aortic valves in animals, digitalis is found to improve the efficiency of the heart, and a smaller mortality occurs in animals under treatment than in the controls.

On the right side of the heart the same action occurs as on the left, and in dilatation of the right heart, such as occurs in some pulmonary

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diseases, digitalis and its allies are beneficial, apparently by increasing the strength of the ventricular contraction.

In the majority of these non-fibrillating cases the pulse is not slowed more than can be accounted for by the rest and general treatment. In a certain proportion, however, distinct slowing is observed as the heart comes under the influence of the drug, or the pause between the contractions of the auricle and ventricle is lengthened; and, as this generally disappears under atropine, it is obviously inhibitory in character in most cases and thus different from the slowing seen under digitalis in auricular fibrillation. The T wave in the electrocardiogram also shows alterations from direct action on the heart muscle.

As regards the irregularities in these non-fibrillating cases, there is no reason to believe that digitalis has any direct action on them, though they may disappear in the course of treatment as the result of the improved nutrition of the heart.

In numerous **acute febrile conditions** the heart becomes affected, possibly in part by the high temperature but largely from the toxic products circulating in the blood. The chief cardiac symptoms are dilatation with a weak systole and a small "fluttering" pulse. In these cases digitalis and other similar drugs may at times be of service in slowing the accelerated heart and in increasing the extent of systole, and thus improving the general circulation. In **pneumonia** more especially, improvement is sometimes seen after digitalis. In this disease, besides the toxic action on the heart, there may be present more or less obstruction of the pulmonary vessels, resulting in overwork and dilatation of the right heart. However, the routine treatment of pneumonia with digitalis is to be deprecated on the general principle that a drug is not to be prescribed until some special indication for it appears; unless distinct evidence of circulatory disturbance is present, digitalis ought to be withheld. As a matter of fact, a study of a large series of cases of pneumonia which had been treated with digitalis, as compared with an equally large group not given this drug, yielded a mortality percentage in favor of the non-digitalized patients. In *diphtheria* the use of digitalis appears to be contraindicated as the drug is unusually toxic in this condition, due apparently to the changes in the heart muscle produced by the toxin. In any case, if it is to be employed, it should be given very carefully.

In acute fevers the inhibitory mechanism is often less irritable than normally, and the activity of the drug must not be estimated by the slowness of the pulse.

In some affections of the heart, such as very extensive fibrous or fatty degeneration, in myocarditis, endocarditis, and arteriosclerotic heart disease, digitalis often is of little or no service, and some authorities deprecate its use, chiefly on the erroneous view that it may raise the blood-pressure and increase the resistance against which the heart has to work. Its failure in these cases is easily understood when one considers that the myocardial musculature is affected, and hence the drug is unable to induce more forceful contractions and an increased cardiac output. In other cases, while the condition of the heart is eminently

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suitable for digitalis treatment, disease of other parts of the body, such as extensive arterial degeneration, is said to preclude its use on account of the danger of rupture of the arterial walls; and many substitute strophanthus for it in these cases in the belief that there is then less risk of the blood-pressure rising to a dangerous height. But as a matter of fact there is no reason to anticipate any extensive rise of blood-pressure under either digitalis or strophanthus, and the apprehension is thus groundless. The same may be said of the supposed danger of digitalis in the high blood-pressure of renal and arterial disease. A high blood-pressure ought not to be regarded as contraindicating the use of digitalis or its allies, for excellent results often follow its exhibition in these cases, provided the special indications for digitalis are presented, in venous stasis, dilatation of the heart, edema, or deficient urine. Digitalis, by increasing the efficiency of the heart, improves the circulation through the lungs and the blood supply of the brain, and the activity of the vasoconstrictor center is abated, leading to a more normal state of the circulation and often to a lower arterial tension.

Recently there has been a tendency to revert to the use of digitalis in certain cardiac conditions other than those in which signs of decompensation are evident. Such patients are diagnosed as suffering from chronic myocardial insufficiency. In these cases with an increased demand upon the heart it is likely to respond by dilatation followed by hypertrophy of the wall. With the hypertrophy the cavities are likely to enlarge still more with stretching of the muscle and still further hypertrophy. A limit to the degree of hypertrophy is finally reached, and signs of cardiac insufficiency may become evident. The early administration of digitalis in these cases before any signs of insufficiency have developed is believed to delay the progress of such changes by retarding the cardiac enlargement and resulting hypertrophy.

In the case of experimental cardiac lesions in dogs digitalis apparently exerts an inhibiting influence upon hypertrophy of the heart (Schwab and Herrmann).

In cases of acute heart failure with paroxysmal nocturnal dyspnea or pulmonary edema with failure of the left ventricle, the use of intravenously injected strophanthin is preferred to digitalis.

The diuretic action of digitalis is not advised except where other indications than a diminution of the renal secretion are present, for in ordinary cases it has much less effect than the xanthine and mercurial diuretics. If the anuria be secondary to disturbances of the circulation, however, digitalis is the diuretic *par excellence* and cannot be replaced by any of the ordinary means of promoting the urinary secretion, although they may advantageously be combined with it. Digitalis and a diuretic of the caffeine or mercurial group are often prescribed together where large accumulations of fluid have to be removed.

Several of these drugs are of considerable benefit in pulmonary diseases accompanied by cough. Thus in bronchitis, more especially in cases of old standing, the addition of squill to an "expectorant mixture" is often followed by the most satisfactory results. The action here is probably twofold. In the first place, the right heart may be dilated

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owing to the frequent strain put on it by coughing, and squill remedies this condition by its usual cardiac action. In the second place, all these drugs possess emetic properties to a certain extent and thus cause an increase in the bronchial secretion and render the sputum less tenacious and more easily expectorated. The addition of squill has the same effect as the prescription of ipecacuanha, along with the further action on the heart.

Contraindications.—There are certain cardiac disorders in which the use of digitalis is definitely contraindicated. Thus in the congestive failure associated with constrictive pericarditis (*concretio cordis*), digitalis, by further reducing the diastolic size of an already constricted heart, reduces the cardiac output and makes worse the condition of the patient. In ventricular tachycardia the use of digitalis in the mistaken view that one is dealing with a tachycardia originating from auricular flutter may be disastrous. Digitalis is also contraindicated in cases of partial heart block, since further interference with the passage of impulses from auricles to ventricles may be harmful. In complete block; however, the use of the drug is not contraindicated. It should not be used in coronary disease except when failure impends or supervenes.

Cumulative Action.—Digitalis is often given in insufficient amount from a dread that it may cause serious results through its cumulative action. This apprehension does not seem to exist so much in regard to strophanthus and squill, though these also induce cumulative effects when they are given in sufficient doses. As a general rule no effects are noted for one or two days after the exhibition of drugs of this series in moderate doses. Improvement then begins if the case is suitable and the dose adequate, and steady progress may be made for some time. Then the symptoms of excessive action may set in suddenly—the pulse becomes alarmingly slow and irregular, the patient complains of weakness and faintness, nausea, and occasionally vomiting. This is known as the cumulative action and is due to the slowness with which the drug is excreted or destroyed. The absorption of the drug given by the mouth is relatively slow, but it is held in the tissues in some form of combination, and thus the concentration tends to increase with each successive dose; this slow elimination is shown by the action continuing for several days after the treatment has been discontinued. As the drug accumulates in the tissues the beneficial action is slowly developed, but if the treatment is continued, a higher concentration is reached and finally becomes equal to that induced by a single poisonous dose and the corresponding symptoms follow. The fear of this condition is much exaggerated, for the symptoms disappear in a day or two if the drug is omitted; and they may generally be avoided altogether if a close watch is kept on the pulse, and the dose is reduced as soon as it becomes slow or at the first appearance of headache, nausea, or loss of appetite. All of the digitalis series hitherto examined prove to be cumulative in their action, but some of them, notably digitoxin, are more dangerous than others.

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Digitalis Intoxication.—Digitalis taken in even large medicinal doses often provokes no symptoms unless the dose is frequently repeated. Poisonous quantities induce nausea and vomiting with abdominal pain and often diarrhea. The patient complains of general depression, headache, giddiness, and precordial discomfort, and often passes into a stage of great muscular weakness and collapse. At times there are also confusion and hallucinations. The pulse first becomes intermittent and then beats regularly at about 40 per minute. Later, it may become rapid and irregular, and fatal coma follows. The symptoms sometimes do not appear until several hours after the poison has been taken and may last for several hours, even days in cases which survive.

A much more common form of poisoning arises from the prolonged use of therapeutic doses. Here the chief symptoms are headache, giddiness, anorexia, nausea and vomiting, visual disturbances, and bigeminal rhythm. More rarely, complete heart block, undue slowing of the heart and, very rarely, auricular fibrillation may occur. It is important not to mistake the nausea and vomiting which may occur as a result of heart failure for that due to digitalis overdosage.

Visual symptoms caused by digitalis intoxication are infrequent. They consist in colored vision, chiefly white, green, yellow, or red flashes of light, colored scotomas, and visual hallucinations. There is no change in the visual acuity (Carroll).

The appearance of any of the above-described symptoms of intoxication necessitates the temporary omission of the drug following which the symptoms disappear, usually within forty-eight hours.

Assay.—The importance of this group in therapeutics is so great that it is to be regretted that no adequate method of chemically estimating the content of active principles is available. The pharmacopeias recognize the advisability of assaying the crude preparations biologically, and the active principles may also be standardized in the same way. Only by using standardized preparations can there be any certainty that the patient is receiving a uniform dose of these drugs.

In the assay of digitalis by the U. S. P. method the dose lethal to the cat is compared with a standard preparation. Attempts have also been made to standardize the drug directly on the human in order to overcome the discrepancy between the lethal effect and the therapeutic effects observed in different preparations.

In recent years much progress has been made in the preparation and marketing of pure glycosides which may eventually replace the use of the crude drugs and eliminate the necessity of bio-assay. Preliminary attempts have also been made to prepare synthetic glycosides which ultimately may be found to exceed the naturally occurring compounds in therapeutic value.

Methods of Administration.—For ordinary purposes the members of the digitalis group are given by the mouth, and the most suitable preparations are pills, capsules, or tablets of powdered digitalis leaf. The tincture is less convenient, more difficult to measure accurately, and subject to deterioration when diluted. Its use is to be discouraged.

Prior to administering digitalis it is important that the physician

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assure himself that the patient has not been taking some form of digitalis preparation, in order to avoid intoxication from an overdose. If none has been taken recently, one pill (0.1 gram, 1½ gr.) orally may be administered four or five times the first day and a similar amount the second day. The average patient will require 15 to 20 pills to effect digitalization, but because of the great variation in the requirement of different patients, it is important to watch closely for desirable or harmful effects after the second day. If none are noted, a similar dose may be continued for the next two days. When the therapeutic effects begin, the daily dose may be reduced gradually until a satisfactory response is evident, after which the patient is kept on a maintenance dose which is continued thereafter. This maintenance dose is usually about 0.1 gram (1 pill or tablet) daily but may vary from 0.1 gram every other day to twice this dose daily.

If the condition of the patient is such that a more prompt effect is desired, digitalis should be given intramuscularly. If no digitalis has been given in previous days, 0.5 gram may be injected deep into the gluteal muscles in one dose. This may be repeated in several hours if circumstances demand. On very rare occasions purified digitalis may be injected intravenously, but the use of crystalline preparations is to be preferred in these cases.

More or less elaborate rules based upon the weight of the patient have been devised to estimate the dose of digitalis to be given, but such figures are at best only suggestive, due to individual susceptibility to the drug. Eggleston suggested weighing the patient and discounting the weight of the edema fluid. The total dose is estimated as 0.1 gram per ten pounds of body weight. Half of this estimated quantity is given as the first dose. Six hours later, if there are no evidences of toxicity, a second dose—one-fourth of the total estimated amount—is given. Subsequently one-eighth of the total amount is given every six to eight hours until the desired therapeutic or toxic effects become apparent.

Digitoxin, the chief glycoside of digitalis is also available in crystalline form for clinical use. All of the essential therapeutic effects of digitalis are produced by digitoxin which has the advantage over the crude drug in being uniformly and completely absorbed from the gastro-intestinal tract. Its dose is, therefore, identical whether given orally or intravenously. Absorption is rapid, occurring in part directly through the stomach wall. A full digitalizing dose may be attained following oral administration within four to ten hours. The emetic action of digitalis which is now believed to be partly central in origin, as already indicated, and in part due to local action in the gastro-intestinal tract is also minimal when the small doses of digitoxin which are required therapeutically are used. The full digitalizing dose of digitoxin, which may be given in a single dose, is 1.2 to 1.5 mg. for the average patient. About 0.2 mg. daily is required for maintenance. Digitoxin is available in tablets of 0.1 and 0.2 mg. and in ampules containing 0.2 mg. per cc.

Because of its erratic absorption from the gastro-intestinal tract,

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strophanthin is administered intravenously. Its effect is demonstrable within a few minutes. It is used where rapid digitalization is desired. It should be injected very slowly in doses of 0.12 to 0.25 mg. Its principal indications are in cases of acute decompensation in which there is no time to wait for the slow action of oral digitalis, as in acute cardiac asthma with paroxysmal dyspnea, acute pulmonary edema of cardiac origin, or acute decompensation during the course of febrile diseases, and in cases where digitalis has failed or cannot be tolerated. It should not be given to a patient who has been receiving digitalis as the two drugs act synergistically, nor should it be used in thyrotoxic heart disease. It is also contraindicated in cases where the ventricular musculature is highly irritable, as evidenced by extrasystoles, since in such cases a fatal ventricular fibrillation may be induced.

Lanatoside C may also be administered intravenously as well as orally. It is efficacious in cases of congestive heart-failure associated with auricular fibrillation (Fahr and La Due). It appears to be less toxic than preparations of digitalis purpurea and may give relief in patients who cannot tolerate sufficient doses of *digitalis purpurea.*

A mixture of the three principal glycosides derived from digitalis lanata **(digilanid)** is also available for oral or intravenous administration.

Preparations

U. S. P.

Digitalis, foxglove, digitalis folium, the dried leaf of *Digitalis purpurea* and assayed to contain 1 U. S. P. digitalis unit in 0.1 gram.

Capsulæ Digitalis, digitalis capsules. Dose, 0.1 gram.

Digitalis Pulverata, powdered digitalis dried and powdered digitalis leaf. Dose, 0.1 gram.

Injectio Digitalis, a sterile solution for injection. Dose, 1 U. S. P. unit.

Tabellæ Digitalis, digitalis tablets. Dose, 0.1 gram.

Tinctura Digitalis, assayed to contain 1 U. S. P. digitalis unit per cc. Dose, 1 cc.

Strophanthinum, strophanthin, glycosides obtained from *Strophanthus kombé*. Dose, 0.0005 gram (1/120 gr.).

Injectio Strophanthini, a sterile solution in water for injection. Dose, 0.5 mg.

Ouabainum, ouabain, a crystalline glycoside derived from *Strophanthus gratus*. Dose, 0.25 mg. intravenously.

Injectio Ouabaini, a sterile aqueous solution of ouabain. Dose, 0.25 mg. intravenously.

B. P.

Digitalis Folium, digitalis leaf.

Digitalis Pulverata, powdered digitalis leaf. Dose, 0.03 to 0.1 gram.

Infusum Digitalis Recens, infusion of digitalis. Dose, 6 to 20 mil.

Tinctura Digitalis, 10 per cent digitalis in 70 per cent alcohol. Dose, 0.3 to 1 mil.

Digoxinum, digoxin. Dose, initially, 0.001 to 0.0015 gram; for maintenance, 0.00025 gram twice daily; by intravenous injection, 0.0005 to 0.001 gram.

Strophanthus, the dried seed of *Strophanthus kombé*.

Strophanthinum–G, ouabain. Dose, 0.00012 to 0.0005 gram intravenously.

Tinctura Strophanthi. Dose, 0.12 to 0.3 mil.

Strophanthinum, a mixture of the glucosides of K–Strophanthin. Dose, 0.00025 to 0.001 gram.

Scilla, squill, the dried bulb of *Urginea scilla*. Dose, 0.06 to 0.2 gram.

Acetum Scillæ, vinegar of squill. Dose, 0.6 to 2 mil.

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EXTRACTUM SCILLÆ LIQUIDUM, liquid extract of squill. Dose, 0.03 to 0.2 mil.

SYRUPUS SCILLÆ. Dose, 2 to 4 mil.

OXYMEL SCILLÆ, oxymel of squill, made with acetic acid and purified honey. Dose, 2 to 4 mil.

TINCTURA SCILLÆ. Dose, 0.3 to 2 mil.

URGINEA, Indian squill. Dose, 0.06 to 0.2 gram.

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L. THE NITRITES

The nitrites have a powerful action on the arteries, in which they cause dilation by depressing the muscle of the walls.

Those which have been examined more carefully are the *Nitrite of Sodium* and the *Nitrous Esters* of the methane series, especially *Amyl Nitrite*, which is largely used in therapeutics. In these compounds the radicle —NO is attached to the metal or alkyl, through an atom of oxygen, the formulæ being Na—O—NO, CH_3—O—NO, C_3H_7—O—NO, C_5H_{11}—O—NO, etc., and the chief constituent is the O—NO, the metal or radicle being of less importance. A closely allied series of bodies are the nitrates, in which the nitrogen has five valencies and is connected again to the metal or radicle by oxygen, Na—O—NO_2, CH_3—O—NO_2, C_5H_{11}—O—NO_2, etc. The inorganic nitrates differ entirely from the nitrites in their effects and are used principally as diuretics (p. 52). Some of the more insoluble nitrates (*e. g.* Bismuth Subnitrate) when given by mouth may be reduced in the gastro-intestinal tract to form nitrites and thus exert the action of the latter. Some of the *Nitric Esters*, however, undergo reduction when brought into contact with organic matter, and nitrites are thus formed, so that these bodies have effects very similar to those of the true nitrites and have to be discussed along with them. The best known of such nitrates is the so-called *Nitroglycerin*, which is really the trinitrate of glycerin, $CH_2(ONO_2)$-$CH(ONO_2)CH_2(ONO_2)$, and is broken up by alkalies into a mixture of nitrates and nitrites. The nitrates have practically no action in the small quantities given, so that almost all the effects of nitroglycerin are due to the nitrite formed. Many other organic nitrates also form nitrites in the tissues but none of them with such rapidity as nitroglycerin. Two which have been used are solids—*Erythrol Tetranitrate* and *Mannitol Hexanitrate*. They act much more slowly and for a longer time than nitroglycerin.

Another series of bodies which may be mentioned as occasionally acting like nitrites, although more feebly, are the nitro-bodies. In these the nitrogen is attached to the alkyl directly, and not through the intervention of an oxygen atom. Examples of these are Nitromethane, H_3C—NO_2, and Nitroethane, CH_3—CH_2—NO_2. Their action is so feeble as to preclude their use in therapeutics and seems due to the —NO_2 being split off in the tissues.

The best known member of the group is **Amyl Nitrite**, and its action will first be described, while the points in which the effects of the other members diverge from it will be discussed later.

Symptoms.—After the inhalation of a few drops of amyl nitrite, the face becomes flushed, and the patient complains of a feeling of fullness and throbbing in the head. Some headache and confusion is often present, the pulse is accelerated, and the respiration is somewhat quicker and deeper. The flush is often confined to the face and neck, but sometimes spreads over the whole trunk, and passes off in a few minutes, unless the inhalation is continued. If large quantities of the drug be inhaled at once, however, or if the inhalation be continued for some time, a feeling of giddiness, weakness, and eventually stupor

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follow, the pulse becomes slow, while the respiration still remains accelerated but is shallower and often somewhat irregular; convulsive movements may occur, but in general large quantities may be taken without actual danger in the human subject. The blood is said to have assumed a dark color in some cases, but this seems to be rare.

Action: Circulation.—The flushing and dilatation of the arterioles of the head are found to be accompanied and followed by a fall in the blood-pressure in man and animals. This is most pronounced in the anesthetized animal. The heart is accelerated and its output increased and therefore is not responsible for the change. The cause, as has been repeatedly demonstrated, is the dilatation of the peripheral vessels, both arterioles and veins widening very considerably under the influence of the drug; the vessels of the abdominal organs and the face are more

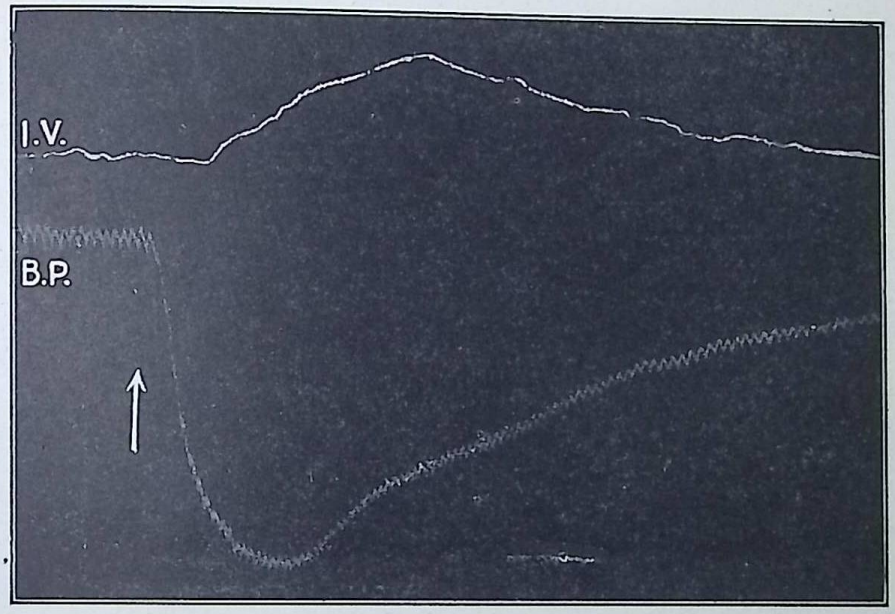

FIG. 63.—Tracing of the blood-pressure (B.P.) and intestinal volume (I.V.) in a cat. Amyl nitrite was inhaled at the point marked with an arrow. The blood-pressure falls while the volume rises from the dilation of the splanchnic vessels.

affected than those of the extremities. The vasomotor center is not concerned in the widening of the vessels, for if amyl nitrite is allowed to pass through the medulla without reaching the peripheral vessels, no fall of pressure occurs. And stimulation of a constrictor nerve such as the splanchnic still produces some rise in the blood-pressure so that the nerve terminations seem to be intact. The seat of action of amyl nitrite is therefore the unstriated muscle of the arteries and veins. No satisfactory explanation has been offered for the fact that in the skin only the vessels of the head and neck should be dilated, but other facts seem to indicate that these vessels occupy an exceptional position as regards their innervation and their reactions to drugs. Darwin was the first to point out that the blush of amyl nitrite corresponds in extent with the blush produced by emotion. This blush effect seems due to the amyl in part, for other amyl esters induce it, though not to the same

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extent as the nitrite. The direct action on the vessel walls may be easily shown by passing blood into the artery of the amputated extremity of an animal and measuring the amount coming from the veins. If a few drops of amyl nitrite are added to the perfused blood, the outflow from the vein is greatly increased, although here no nervous mechanism can be concerned.

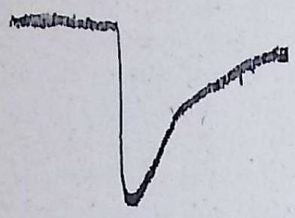

FIG. 64.—Blood-pressure under amyl nitrite taken on a slow drum in order to demonstrate the recovery. The whole tracing occupied some six minutes. The rapid fall of pressure is followed by an almost equally rapid return to normal. (Cash and Dunstan.)

The acceleration of the pulse is more marked in man and the dog than in other animals and is the result of the fall in blood-pressure which reflexly depresses the tone of the inhibitory cardiac center and excites the accelerator apparatus. The coronary arteries of the heart are dilated along with those of other parts of the body, with an augmentation of the blood supply to the heart despite the drop in systemic pressure.

In man the depressor effects of amyl nitrite and the other nitrites is much less striking than in the anesthetized animal. In fact with therapeutic doses an appreciable drop in pressure is observed only in about half of individuals, the remainder showing no or only minimal reductions in blood-pressure despite the vasodilation which these substances induce. The maintenance of the normal blood-pressure is made possible by the compensatory increase in cardiac output which accompanies the vasodilation. It is only when the dilation is excessive and the heart is unable to maintain an adequate output that the blood-pressure drops.

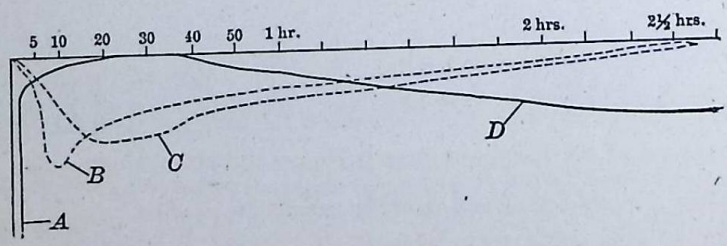

FIG. 65.—Diagram to illustrate the intensity and duration of the action of the members of the nitrite series. The extent of the fall of pressure is measured along the vertical, the duration along the horizontal line. *A*, amyl nitrite, ethyl nitrite, etc.; *B*, nitroglycerin; *C*, sodium nitrite; *D*, erythrol tetranitrate. The greatest fall in pressure occurs in *A*, but it passes off for the most part in five minutes and entirely in twenty. Nitroglycerin acts more rapidly than the last two, and its effects continue almost as long as those of sodium nitrite. Erythrol tetranitrate only exerts its full effect after the action of the others has passed off. (After Bradbury.)

The increased cardiac output observed following the administration of amyl nitrite is accompanied by a decrease in the systolic output, *i. e.* in the amount of blood expelled with each heart beat. The acceleration of the heart rate, however, is out of proportion to the decrease in systolic output so that the end-result is an increased output per minute. In conditions in which the ventricular rate does not increase following the administration of amyl nitrite, as observed, for example, in some

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cases of complete heart block, it is questionable if the administration of the drug will result in an increased cardiac output as a compensation for the lowered blood-pressure.

Large quantities of amyl nitrite slow and weaken the contractions of the heart, owing to a direct depressing action on the muscle. In the frog, the heart is usually slowed from the beginning of the application.

The **Respiration** is generally accelerated and at the same time rendered deeper by amyl nitrite.

Not infrequently the breath is held at first, owing to a reflex from the nasal mucous membrane, but this is not so marked as in the inhalation of more irritant vapors, such as chloroform or ether. The acceleration is the result of the fall in pressure lessening the supply of blood to the brain and arousing the respiratory center. After long inhalation the respiration becomes slower and shallower, and in animals death occurs from asphyxia. The walls of the pulmonary vessels are less affected by the nitrites than those of the systemic circulation, and any change which occurs in the pulmonary blood-pressure is probably the indirect result of the acceleration of the heart. The bronchial muscle is apparently relaxed by the inhalation of amyl nitrite or by the administration of other members of the group by the stomach, for relief is given in asthma. An old method of inducing this effect is by burning paper impregnated with saltpeter and inhaling the fumes, which contain nitrite formed by the reduction of the nitrate.

The **Kidneys** are not much affected by this series; occasionally a slight increase in the urine is observed, at other times a decrease, and after large quantities anuria may occur. These effects are evidently due to the changes in the caliber of the renal vessels. A small quantity may widen them when they are too contracted to allow of the maximal secretion, while on the other hand, if the normal caliber is the optimal, a nitrite may lessen the secretion by lowering the general blood-pressure. When large quantities lower the pressure, they inevitably lead to a lessened secretion or anuria.

Small quantities of amyl nitrite seem to have no action whatsoever on the higher parts of the **Central Nervous System.** The throbbing in the head and slight confusion are evidently due to the fall in general blood-pressure. The sight is curiously affected in some people, for when a dark object on a white background is looked at, it seems surrounded by a yellow ring and that again by a blue one. In the beginning the medullary centers may be slightly acted on reflexly from irritation of the nasal sensory terminations, and later the fall in blood-pressure and consequent anemia of the medulla lowers the activity of the inhibitory center for the heart and stimulates the respiratory and vasomotor centers. The spinal cord is not acted on in mammals but is depressed in the frog.

After large quantities convulsions are often observed; these seem to be of cerebral origin, and are probably due to the circulatory changes and the formation of methemoglobin.

The **Peripheral Nerves** and the **Muscles** are unaffected by the inhalation of amyl nitrite, but when the frog's muscles are exposed to the direct

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action of the vapor, they undergo a slow, passive shortening and rigor, and on periodical stimulation the contractions become rapidly weaker, until finally no response is made to the electric shock. Involuntary muscle is more easily affected than striated fibers, as has been shown by the behavior of the intestine and ureters, but even these seem less readily paralyzed than the muscle of the vessel walls, the depression and paralysis of which lead to the fall in the arterial tension, as has been already stated. The nerve terminations seem to be unaffected even by very large quantities, so that as long as a contraction of the muscles can be elicited by direct stimulation, it follows also on stimulation of the motor nerve, and the vagus terminations in the heart can transmit impulses so long as the heart continues to beat. The **Temperature** is somewhat lowered by the nitrite series, owing to the dilatation of the skin vessels, but this fall is insignificant.

During the fall in the blood-pressure, the **Blood** is diluted by the lymph pouring into it from the tissues, while as the pressure rises the concentration returns to the normal. The nitrites change the hemoglobin to methemoglobin and nitric-oxide-hemoglobin, giving a dark chocolate color. This does not entail the destruction of the red corpuscles, and the compounds are eventually reduced by the tissues, although the reduction progresses much more slowly than that of ordinary oxyhemoglobin. In man, usually very little of the hemoglobin is thus transformed, and even after large quantities have been inhaled no abnormal coloration of the blood is noticeable, but the alteration of the hemoglobin is the cause of death in some animals, through the blood becoming incapable of carrying oxygen to the tissues. If, however, asphyxia be prevented by the inhalation of oxygen under pressure, the tissues themselves are eventually acted on. The formation of methemoglobin does not seem to bear any relation to the action of the nitrites on the vessel walls and is identical with that caused by other reducing bodies, which have no action on the blood-vessels.

Excretion.—After absorption into the blood, amyl nitrite seems to break up with the formation of nitrites of the alkalies. These undergo partial oxidation and appear in the urine in the form of nitrates and nitrites, but the quantity of these excreted is never equal to the nitrite absorbed, so that it seems probable that some part undergoes still further change. The amyl disappears and is probably oxidized completely, although some may appear in the breath.

Nitrite of amyl given by the stomach is much less active than when inhaled, as the nitrous acid is freed by the gastric juice and immediately decomposed. When injected subcutaneously it acts much more slowly and weakly than when absorbed by the lungs, and generally gives rise to glycosuria and slight diuresis.

The pharmacopeial **amyl nitrite** is a yellow, very volatile fluid, with a strong, fruity odor, soluble in alcohol and ether but rapidly decomposed by water. It consists of the nitrite of iso-amyl for the most part, along with small quantities of the nitrites of butyl, propyl, etc. Two to five drops are poured on a handkerchief and inhaled. A convenient preparation is the amyl nitrite "pearls," which are thin glass capsules, each

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containing a dose of the remedy, and one of which is broken in the handkerchief when necessary. Amyl nitrite is liable to decompose when kept for long, and ought to be used only when recently prepared.

Sodium Nitrite resembles the organic nitrites closely in action. It is administered by the stomach, and therefore acts more slowly than amyl nitrite, but its effects last much longer. The gastric juice liberates part of the nitrous acid before absorption can occur, and it is immediately decomposed and often causes some eructation and may also give rise to irritation of the gastro-intestinal mucous membrane. The nitrite absorbed is excreted as nitrate in the urine, although some of it may remain unoxidized. The inorganic nitrites do not as a rule cause so much headache and flushing of the face and neck as the alkyl compounds.

Nitroglycerin produces the same effects as the other members of this series, but acts more powerfully than either the inorganic or alkyl nitrites. It presents some minor points of difference, as in causing more severe headache in man. It is not decomposed in the stomach, but on reaching the blood at once breaks up into glycerin, nitrites and nitrates. Its action commences very soon after its administration, and lasts much longer than that of amyl nitrite. The explanation of its greater activity may be that it is absorbed unchanged, but is then broken up at once, while the inorganic nitrites are decomposed in the stomach and much of the nitrous acid is lost. Nitroglycerin is not wholly broken up in the human body, however, for it has been found in the urine, and the headache which so frequently follows its administration in man has been ascribed to the undecomposed molecule, and not to the nitrite constituent. Nitroglycerin disappears very rapidly from the blood of dogs following its intravenous administration. Within one minute an average of only from 10 to 15 per cent of the amount given is detectable as remaining in the blood and none can be found at the end of from fifteen to twenty minutes. It is generally supposed to be extremely poisonous, and is prescribed in minute doses, but it has been shown that while very small quantities are sufficient to produce therapeutic effects in man, the toxic dose is enormous in animals. Except in individuals who manifest a hypersensitivity to nitroglycerin, the repeated administration of therapeutic doses does not induce toxic effects.

A certain degree of **tolerance** to the nitrites is gained by man from their repeated administration. Especially is this true as regards the headache which they often produce, whereas tolerance is not so easily produced against their vascular effects. Also, a fairly complete cross tolerance apparently exists between the different members of the series.

Glyceryl trinitrate or nitroglycerin is used in the form of the **spirit of nitroglycerin**, an alcoholic solution containing 1 per cent of glyceryl trinitrate, and in the form of tablets, containing 0.3, 0.4, 0.6 and 1.2 mg. (1/200, 1/140, 1/100 and 1/50 gr., respectively) of the drug. It is most conveniently administered by application of a tablet (0.3 mg.) under the tongue.

Several other organic nitrates have also been found to reduce the blood-pressure. Their decomposition proceeds more slowly than that

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of nitroglycerin and hence their action is prolonged. **Erythrol tetranitrate** and **mannitol hexanitrate** are available in the form of tablets. The former is administered in doses of 30 to 60 mg., the latter in doses of 15 to 30 mg. every four to six hours. The use of these drugs is often attended with severe headache. Other toxic effects include the formation of methemoglobin, a rise in intra-ocular pressure and cardiovascular collapse.

Ethyl nitrite was formerly used in the form of a 4 per cent alcoholic solution (sweet spirits of niter). When freshly prepared it acts like the other nitrites, but when prescribed along with water, as is usually the case, the nitrite escapes rapidly, and it has little effect except from the ether and alcohol.

Therapeutic Uses.—The nitrites were introduced into therapeutics by Brunton, who advised their use in **angina pectoris** to relieve spasm of the arteries. Since amyl nitrite also often gives relief in cases in which the blood-pressure is not elevated the mechanism of its action in relieving the pain of angina pectoris must be attributed to the dilatation of the coronary arteries which the drug induces. For rapid, transient effects amyl nitrite seems especially indicated, while nitroglycerin and nitrite of sodium are more suited to produce a depression of some duration. Thus during the attack of angina pectoris, amyl nitrite is often found to give instant relief, but if nitrite of sodium or nitroglycerin is administered every four to six hours, no attack may occur. The disadvantage of the inorganic nitrites is the frequent eructation they produce, while nitroglycerin often causes severe headache, which, however, disappears in some cases after repeated use or when used in minimal doses. The pulse assumes the dicrotic character under all of the nitrite series, owing to the reduced peripheral resistance (Fig. 66).

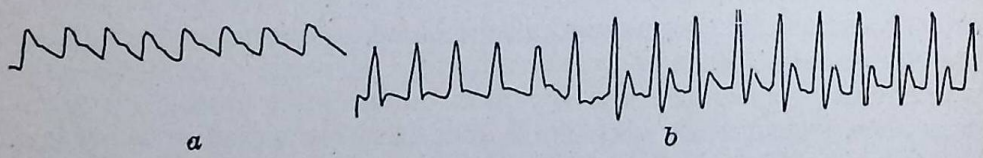

FIG. 66.—Pulse tracing in a case of angina pectoris: *a*, before; *b*, during the inhalation of amyl nitrite.

The nitrite series may also be used in any condition in which dilatation of the blood-vessels is desirable. Its beneficial effects are not due to any direct action on the heart, but to the increased blood supply to the tissues. Thus in epilepsy the inhalation of amyl nitrite during the aura which precedes a convulsion may abort an attack through the better vascularization of the brain which it induces.

The nitrites, particularly the long acting ones, have been advocated for the treatment of hypertension. However, their use in this condition has met with little success since not only do they induce a lesser drop in blood-pressure than is observed in the normal, but this drop when it occurs is accompanied by undesirable reactions. Moreover, any reduction in blood-pressure induced by such non-specific measures would appear to be irrational on the basis of our present concepts regarding the mechanism of the disorder. As a matter of fact, the observed lower-

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ing of the blood-pressure is not striking and is confined principally to the systolic pressure, the diastolic being only lowered a few millimeters at most.

In very advanced degeneration of the cardiac muscle fiber, the administration of the nitrites is distinctly contraindicated, for the blood-pressure is low, and any further reduction may lead to syncope from anemia of the brain.

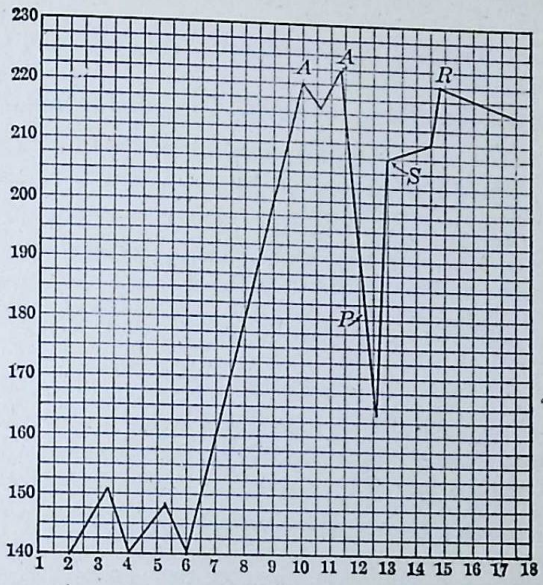

FIG. 67.—Blood-pressure chart during an attack of angina pectoris. The pressure, originally 140 to 150 mm. of mercury, rapidly rose to 220, and intense pain was present over the heart. At *A* and *A*, amyl nitrite was inhaled and the pressure fell to 165 mm. At *P* the pain had disappeared. The pressure rose again rapidly and at *S* the pain recurred slightly and was very severe at *R*. Time in minutes.

Nitrite of amyl has been used largely in asthma and in cardiac dyspnea. Its action is often beneficial and has been attributed to its depressing the bronchial muscles, which are believed to be in a condition of spasmodic contraction in asthma. In the cardiac cases its action in removing the dyspnea may be due to its lowering the pressure in the systemic arteries and thus relieving the heart.

In some cases of headache, nitrite of amyl is of marked benefit, while in others it aggravates the condition. This is perfectly intelligible, as some forms of headache may be due to cerebral congestion and peripheral constriction, while others arise from anemia of the brain.

The action and employment of nitrites as antidotes in cyanide poisoning is discussed on page 665.

PREPARATIONS

U. S. P.

AMYLIS NITRIS, amyl nitrite, a clear, volatile liquid. Dose, 0.2 cc. (3 min.).

SPIRITUS GLYCERYLIS TRINITRATIS, spirit of glyceryl trinitrate, 1 per cent glyceryl trinitrate in alcohol. Dose, 0.06 cc. (1 min.).

TABELLÆ GLYCERYLIS TRINITRATIS, tablets of nitroglycerin. Dose, 0.4 mg. (1/150 gr.).

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Sodii Nitris, sodium nitrite. Dose, 60 mg.

Tabellæ Erythritylis Tetranitratis, erythrityl tetranitrate tablets. Dose, 30 mg.

B. P.

Amylis Nitris. Dose, 0.12 to 0.3 mil. (2 to 5 min.).

Liquor Glycerylis Trinitratis, 1 per cent of glyceryl trinitrate in 90 per cent alcohol. Dose, 0.03 to 0.12 mil. (½ to 2 min.).

Tabellæ Glycerylis Trintratis. Dose, 0.0005 to 0.001 gram.

Sodii Nitris. Dose, 0.03 to 0.12 gram (½ to 2 gr.).

Spiritus Ætheris Nitrosi, sweet spirit of niter. Dose, 1 to 4 mil. (15 to 60 min.).

Liquor Æthylis Nitritis Concentratus, concentrated solution of ethyl nitrite. Dose, 0.125 to 0.5 mil.

Tabellæ Erythritylis Tetranitratis. Dose, 0.015 to 0.06 gram.

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M. MINOR DRUGS AND POISONS

I. MISCELLANEOUS DRUGS

1. Chaulmoogra Oil

Chaulmoogra oil is a fatty oil expressed from the seeds of *Taraktogenos kurzii*, a tree growing in Burma and adjacent countries. An oil having similar chemical and therapeutic properties is also obtained from the seeds of *Hydnocarpus wightiani*, *H. anthelmintica* and other species of *Hydnocarpus*. It has long been used, especially in China, as a remedy for leprosy, but, given by mouth, it produced so much nausea and gastric irritation that it was not possible to give effective doses. With better knowledge of the nature of the active principles of the oil and improvements in its preparations, it became possible to administer such preparations by injection with more encouraging results.

Chaulmoogra oil consists chiefly of the glycerides of a group of unsaturated fatty acids which are optically active and possess a closed five-carbon ring. The most important of these are hydnocarpic acid and chaulmoogric acid. The latter compound possesses twelve instead of ten CH_2 groups in the side chain as in hydnocarpic acid and is more abundant in the oil but is believed to be less potent therapeutically.

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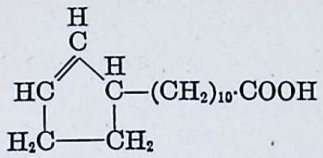
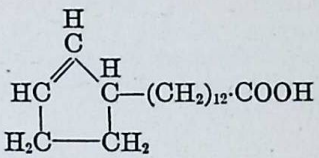
In 1913 Heiser reported apparent cures of leprosy from intramuscular injections of the oil. This was a distinct advance but had the serious drawback that the injections were painful and liable to produce local necrosis. Rogers got better results from the use of sodium salts of the acids by subcutaneous or intravenous injection, and Dean introduced treatment by intramuscular injection of ethyl esters.



Hydnocarpic acid



Chaulmoogric acid

Though, owing to the very chronic nature of the disease and the fact that spontaneous remissions are of common occurrence, the estimation of the value of remedies is slow and difficult, reports from leper institutions in different parts of the world indicated that derivatives of chaulmoogra oil in certain cases checks the disease and possibly affects a cure in some early cases. Treatment must be carried out for months or even years.

In 1920 Walker and Sweeney showed that, in respect to acid-fast bacilli and these only, sodium salts of chaulmoogra acids are 100 times more powerfully bactericidal than phenol. It is supposed that this remarkable bactericidal action is due to the action of the unsaturated acids upon the waxy envelope of acid-fast bacilli and that this underlies the efficacy of chaulmoogra acids in leprosy.

Among other **toxic** actions which are liable to occur from chaulmoogra oil or its derivatives are nausea and emesis (from local irritant action on the stomach but also from central action), hemolysis, renal irritation, and fatty infiltration of the liver. Continuous administration of small doses favors calcium retention, while large doses increase calcium excretion and diminish the blood calcium.

Rogers has used other unsaturated acids in leprosy and has reported favorable results with **sodium morrhuate**, the sodium salt of the unsaturated fatty acids of cod-liver oil. A number of related synthetic compounds have also been tried without success.

Promin, one of the sulfonamide derivatives described later (p. 731), has also been used in the treatment of leprosy with promising results.

A 5 per cent solution of sodium gynocardate or a solution of the sodium soap of chaulmoogra oil is used as a **sclerosing** agent to produce thrombosis in varicose veins. It is said to be superior to the 5 per cent solution of sodium morrhuate for this purpose. The injection of 2 cc. of chaulmoogra oil solution will result in thrombosis of a vein for a distance of about 5 cm. (Ochsner).

Preparations

U. S. P.

Oleum Chaulmoogræ, the fixed oil expressed from the seeds of Taraktogenos kurzii or from certain species of Hydnocarpus; a yellow or brownish-yellow liquid, with characteristic odor and acrid taste. Dose, 1 cc. (15 min.).

Æthylis Chaulmoogras, ethyl chaulmoograte, the ethyl esters of the fatty acids of chaulmoogra oil. A clear, pale yellow liquid, having a slight fruity odor. Insoluble in water. Dose, 2 cc. by mouth or intramuscular injection.

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B. P.

OLEUM HYDNOCARPI, the fatty oil obtained from the seeds of Hydnocarpus wightiana. Dose, 0.3 to 1 mil. increasing gradually to 4 mil.; by subcutaneous and intramuscular injection, 2 mil., increasing gradually to 5 mil.

OLEUM HYDNOCARPI ÆTHYLICUM consists mainly of ethyl esters of chaulmoogric and hydnocarpic acids, a colorless or yellowish limpid oil, with characteristic odor and slightly acid taste. Doses as in preceding preparation.

SODII MORRHUAS, sodium morrhuate, a mixture of the sodium salts of fatty acids obtained from cod-liver oil.

INJECTIO SODII MORRHUATIS, injection of sodium morrhuate. Dose, intravenously, as a sclerosing agent, 0.5 to 5 mil.

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2. Aconitine and Related Alkaloids

This series embraces a number of alkaloids which resemble each other closely in their chemical and pharmacological properties. They are found in a number of species of the Aconitum genus, the best known of which are Aconitum napellus, containing *Aconitine* ($C_{34}H_{47}NO_{11}$), Aconitum ferox, *Pseudaconitine* ($C_{36}H_{51}NO_{12}$), and Aconitum japonicum, *Japaconitine* ($C_{34}H_{49}NO_{11}$). Aconitum napellus is the common garden plant known as monkshood, in allusion to the cowl-shaped posterior sepal of its flower, or wolfsbane, because of its use in poisoning bait for destruction of wolves.

Another alkaloid which resembles aconitine closely in its pharmacological action is *Delphinine* ($C_{31}H_{49}O_7N$). It is found in stavesacre (Delphinium staphisagria), along with a number of other bases (delphisine, delphinoidine), which may be the products of its decomposition. The crushed seeds of stavesacre have been used since ancient times for the destruction of head lice but have been replaced by less dangerous preparations.

The symptoms caused by aconitine, pseudaconitine, japaconitine, and delphinine are very similar, differing mainly in degree and not in kind. Pseudaconitine is more poisonous than japaconitine which in turn is slightly more active than aconitine. Delphinine is much less poisonous.

Symptoms.—After very large quantities of aconitine death may result instantaneously, apparently from simultaneous failure of the heart and central nervous system.

If smaller quantities be swallowed, there is noted, after the ordinary bitter taste of the alkaloid, a feeling of warmth in the mouth and throat, which agreeable at first, soon becomes prickling and tingling, and extends to the stomach and eventually to the skin. This is accompanied by a profuse flow of saliva and often by vomiting. The pulse is very slow and may be irregular, and later becomes weak and imperceptible when symptoms of collapse appear. The respiration is slow and labored, and great muscular weakness is complained of. After a time the smarting and tingling of the skin are no longer felt, and on examination the cutaneous sensibility is found to be much reduced. The intelligence remains unimpaired to the last in many cases, although unconsciousness sometimes occurs, and death is generally, but not invariably, preceded by convulsions. The pupil is unaffected except when convulsions supervene, when it is

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dilated. The prickling of the throat and skin is the most characteristic symptom, and is practically diagnostic in cases of poisoning, no other drug excepting veratrine having this effect. Death is sometimes due to paralysis of the respiratory center from the direct action of the poison, but in other cases the heart fails before the respiration.

Action.—The prickling, tingling sensation is due to an affection of the **Terminal Organs of the Sensory Nerves**, as is shown by its appearing first at the point of application of the drug. But no redness or swelling of the skin is induced, nor are blisters formed, so that aconitine differs entirely from the class of skin irritants (p. 197). It evidently acts by stimulating the terminations of the sensory nerves, more especially those of common sensation, while the other sensory end organs have not been shown to be involved. Evidence of the stimulation of **Other Terminations** is presented in fibrillary twitching of the muscles in the frog and sometimes in mammals. This is prevented by curare, but not by section of the nerves, and is therefore attributed to stimulation of the terminations of the motor nerves in muscles.

Circulation.—After small quantities, the heart does not seem to be affected in man, while in maximal therapeutic amounts it is very often accelerated through the nausea induced by the irritant effect in the stomach. In cases of poisoning the heart is very slow and irregular due to stimulation of the inhibitory center in the medulla.

In large doses aconitine exerts a further, direct action on the heart, which suddenly accelerates from the slow vagus rhythm to one far above the normal. Soon irregularities of many different forms follow, one of the most common being reversal of the beat, in which the ventricle contracts before the auricle and gives the rhythm to the heart.

The **Respiration** is early affected in aconitine poisoning; it becomes much slower, the movements are labored, and the animal suffers from marked dyspnea.

Central Nervous System.—The higher centers seem to be almost unaffected by the drug, for consciousness has often remained to the end, and when this is not the case, the mental symptoms are to be ascribed to the changes in the heart and respiration.

The **Secretion** of saliva is greatly increased by aconitine, from the irritation of the sensory terminations in the mouth and from the nausea.

Aconitine sometimes reduces the **Temperature** both in fever and in normal animals, but the precise way in which this action is elicited is unknown.

In cases of **Poisoning** in animals, atropine has been found to alleviate the symptoms and not infrequently to lead to recovery after doses which would otherwise have been fatal.

Aconitine is **Excreted** mainly by the urine. Minute quantities have also been found in the saliva and bile.

Benzaconine is much less poisonous than aconitine and, in fact, can scarcely be included among active poisons, though large quantities act on the heart, slowing it and rendering it irregular, and also depress the respiration. It has no effect on the sensory terminations. **Aconine** itself is almost inactive but large quantities strengthen the heart beat and paralyze the terminations of the motor nerves like curare.

The alkaloids obtained from some other species of *Aconitum* have been found to differ considerably from aconitine and pseudaconitine in their action. *Lappaconitine* causes clonic convulsions, vomiting, dyspnea and finally paralysis of the respiration and heart, and in the frog lessens the sensibility of the skin. *Septentrionaline* does not cause poisoning when taken internally, but injected subcutaneously induces local anesthesia and later paralysis of the motor terminations, like curare. *Cynoctonine* is also inactive when swallowed and is less poisonous than the others when applied by hypodermic injection, when it causes tonic and clonic convulsions which are not generally followed by paralysis. Two alkaloids, *lycaconitine* and *myoctonine*, have been found in Aconitum lycoctonum, and induce almost identical symptoms. They increase the reflex excitability, and this is followed by convulsions and later by paralysis of the terminations of the motor nerves and by failure of the heart.

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Therapeutic Uses.—The action of aconitine on the sensory nerve terminations suggested its local use in cases of neuralgia. Aconitine is the most poisonous of the alkaloids, 0.2 mg. taken by the mouth inducing distinct symptoms in man; and its use in therapeutics should be discouraged.

PREPARATIONS

B. P.

ACONITUM, aconite.
LINIMENTUM ACONITI, liniment of aconite.

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3. Veratrine

A number of alkaloids have been found in species of Veratrum and allied genera, and resemble aconitine in their pharmacological action. **Veratrine** is found in the seeds of *Schœnocaulon officinale* or *Asagræa officinalis* (sabadilla or cevadilla seeds) and also in *Veratrum sabadilla* and *Veratrum viride* or Green Hellebore. Hellebore is also the popular name of Helleborus niger, which differs entirely from Veratrum in its principles and also its action. Veratrine is a mixture of two alkaloids, *cevadine* and *veratridine*. The chief alkaloid of Veratrum album, White Hellebore, is *protoveratrine*. Alkaloids of this series have been found in several species of *Zygadenus*, the Death Camas, which is an important cattle poison in the Western United States.

Each of these alkaloids is accompanied by a number of others, most of which are imperfectly investigated chemically and pharmacologically. In cevadilla, in addition to *Veratrine*, there are found *Cevadilline*, *Sabadine*, *Sabadinine*, and *Sabatrine*. In white hellebore *Protoveratrine* is accompanied by *Jervine*, *Pseudojervine*, *Rubijervine*, *Protoveratridine*, and others. Green hellebore contains *Cevadine*, *Jervine*, *Pseudojervine* and *Veratridine*.

Action.—The effects of veratrine resemble those of aconitine very closely in their general character and particularly in regard to the sensory terminations; but the muscles present a curious reaction to veratrine, which is entirely absent in aconitine poisoning.

The symptoms differ from those of aconitine only in the greater tendency to colic and purging under veratrine, and in the presence of fibrillary twitching of the muscles and convulsions in the later stages of poisoning.

The prickling of the skin is a striking feature of veratrine poisoning, and the same action leads to violent sneezing and coughing when small quantities of veratrine come in contact with the sensitive mucous membranes of the nose and throat. After the irritant action has lasted for some time, the sensory terminations in the skin become less sensitive, and a feeling of numbness and cold is noted.

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The most characteristic action of veratrine is that on the **Striated Muscles.** If a small quantity be injected into the lymph-sac of a frog, a curious clumsiness and awkwardness in the movements becomes apparent, and after a few minutes it is evident that this is due to inability to relax its muscles. When a muscle is exposed, it is seen to contract as rapidly as usual, but instead of immediately relaxing again, it remains shortened and offers resistance to the contraction of the opposing muscles. The animal can therefore no longer coördinate its movements; for example, it can no longer extend a limb immediately after flexing it, as it does ordinarily in crawling, and locomotion becomes very slow and ungainly.

This characteristic action is most easily seen on exposing an excised frog's muscle to a solution of veratrine; as long as the muscle remains at rest no change is seen, but on stimulating it with a single induction shock, it is found that the height of the contraction is increased and the second part of the curve is extraordinarily prolonged (Fig. 68). Instead of the almost instantaneous return to the base line seen in the normal tracing, the curve shows generally a slight undulation, and then a very slow fall, the period of relaxation generally being twenty to thirty times as long as that in the unpoisoned muscle, and the whole contraction lasting five to ten seconds in favorable circumstances.

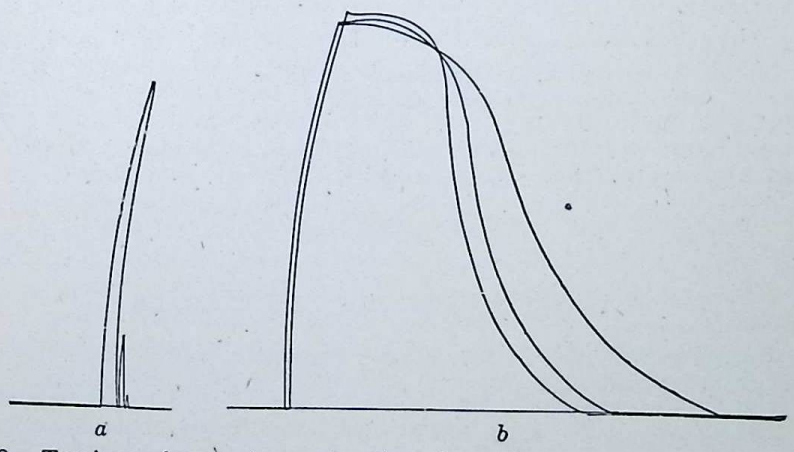

FIG. 68.—Tracings of muscular contractions from the gastrocnemius of the frog. *a*, normal; *b*, three successive contractions taken at intervals of one minute, five minutes after the injection of veratrine. The contraction is higher and much more prolonged than in *a*, and the lever returns very slowly to the base line.

Certain phenanthrene derivatives, formed by substituting various chemical groups on the 9-carbon atom, produce a veratrine-like action on mammalian skeletal muscle.

The **Nerve** fibers are paralyzed by veratrine directly applied to them, and also by protoveratrine, though less powerfully.

Circulation.—The ventricular systole of the frog's heart is at first stronger and more prolonged, and soon it dilates only half as often as it did at first, while the auricles maintain their original rhythm. This is evidently due to action on the muscle; the contraction is so prolonged as to limit the number of diastoles, and the ventricle can therefore react only to every alternate contraction of the auricle. After this "half-rhythm" has persisted for some time, the contractions become slower and weaker, and the heart finally comes to a standstill.

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In mammals the changes in the circulation resemble those under aconitine except that larger amounts of veratrine are required to produce the same effects and the more obvious symptoms of stimulation of the myocardium are not elicited.

As regards the other alkaloids of this series, jervine, sabadilline, and sabadinine seem to possess the same action as veratrine, but are much less poisonous. Protoveratrine, which has less stimulant effect on the sensory terminations and on the muscle fibers, is more poisonous, its action resembling that of aconitine as much as that of veratrine.

Therapeutic Uses.—Veratrine is used in the form of the oleate or ointment as an external application in cases of neuralgia and is certainly a safer remedy than aconite. Veratrum album has been used to reduce the pulse rate and the blood-pressure, but its effects are minimal and the drug is no longer used for this purpose.

The chief use of Veratrum viride at present is in the treatment of **eclampsia.** In this condition it is given in doses of 0.3 to 0.6 cc. every fifteen minutes until the pulse rate drops below 60 or the systolic blood-pressure below 120. As long as the patient remains unconscious doses of 0.2 to 0.6 cc. are given whenever the pulse rate rises above 80 or the blood-pressure above 150.

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4. Saponin, Sapotoxin and Solanine

This group comprises a series of glycosides which are very widely distributed in plants and which resemble each other in certain reactions with living cells. The most poisonous among them are designated by the general term of Sapotoxins, while Saponin may be used to include the less active and the wholly innocuous members of the group.

These glycosides reduce the surface tension of water to a very marked degree, and even dilute solutions form froths like soap when shaken up. From this property the plants derive their popular names of soap-root or soap-bark. The reduction of the surface tension also explains their property of holding insoluble bodies in suspension. The saponins have a peculiar affinity for lecithin, which they dissolve, while cholesterol forms an insoluble chemical compound with many of them; they tend to be deposited on the surface of cells with which they come in contact.

Saponins or sapotoxins are found in many species of plants. The chief of these are: *Quillaja saponaria*, or soap-bark; *Saponaria officinalis*, or soap-wort; *Cyclamen Europeum*, or sowbread; *Polygala senega; Agrostemma githago*, or corn-cockle; *Gypsophila struthium* and other species; *Chamælirium luteum*, or blazing star; *Smilax*, various species, including those known as sarsaparilla.

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In addition, a number of drugs contain saponins along with other more important principles. Thus digitonin, gitonin and tigonin are met with in digitalis purpurea.

Another body closely resembling the saponins in action is *Solanine*, a glucosidal alkaloid found in many species of *Solanum*, such as *S. nigrum* (black nightshade), *S. dulcamara* (bittersweet), *S. tuberosum* (potato), and probably in some species of *Scopola*. Solanine breaks up on being heated with acids into sugar and a base, *Solanidine*, which retains the poisonous action. Some interest attaches to solanine from its having been held responsible for some instances of widespread poisoning from the use of potatoes. But it is now known that the symptoms arose from putrefactive bacteria and their products, and that solanine is never present in the tuber of the potato in sufficient quantity to be noxious.

Chemistry.—The saponins are glycosides which on acid hydrolysis are split into glucose and other sugars and steroid derivatives designated as **Sapogenins**. The latter contain two heterocyclic oxygen rings in the side chain attached to Carbon-17 of the steroid nucleus.

Action.—The sapotoxins have a harsh, acrid, taste, and when swallowed provoke nausea and often vomiting, with pain and colic, and less frequently diarrhea. They are not absorbed by the normal epithelium of the alimentary canal, and seem to undergo decomposition in the bowel, and therefore fail to produce general symptoms. Thus pigs feed with avidity on cyclamen and are unharmed by it unless some lesion of the intestine is present. The unbroken skin is not affected by a single application as a general rule, but when they are applied repeatedly or rubbed in as ointment, they cause irritation and pustules. Absorption is extremely slow from the cutaneous tissues, in which they act as irritants, however, and produce inflammation and suppuration. The sapotoxin derived from agrostemma differs from the others in being absorbed fairly rapidly from the alimentary canal and from the subcutaneous tissues, so that more dangerous symptoms may arise from it than from the other members of the series. When these bodies are injected directly into the blood-vessels, they induce much more characteristic changes, which very often prove fatal after a longer or shorter interval.

When the individual organs are exposed to the action of saponin bodies by the direct application of solutions to them, a similar poisonous action is elicited. Muscle contracts more weakly even in dilute solutions, is eventually entirely paralyzed, and is altered in structure, the transverse striæ of voluntary muscle and of the heart becoming very indistinct. Nerves exposed to solutions are also paralyzed in the same way, and the movements of cilia cease at once when they are exposed to sapotoxin bodies. The blood undergoes characteristic changes when it is acted on by saponin, either in the vessels or in the test-tube. The red blood cells undergo rapid destruction, and the hemoglobin is freed in the plasma. Even 1 part of cyclamen added to 100,000 parts of diluted blood completely lakes the red blood cells, while hemoglobin appears in the serum when considerably less poison is added.

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5. Hydrastine and Hydrastinine

Hydrastine is an alkaloid which occurs in Hydrastis canadensis (Golden Seal) along with two other alkaloids, *Berberine* and *Canadine*.

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Hydrastine ($C_{21}H_{21}O_6N$) is readily decomposed into *Hydrastinine* ($C_{11}H_{12}O_2N$) and opianic acid. Chemically hydrastine is nearly related to *Narcotine* ($C_{22}H_{23}NO_7$), one of the opium alkaloids, which differs from it only in the possession of another methoxyl group; and narcotine can also be decomposed into *Cotarnine* ($C_{12}H_{15}NO_4$) and opianic acid, cotarnine differing from hydrastinine again only by a methoxyl. Another opium alkaloid, *Laudanosine*, undergoes a similar decomposition and the resulting alkaloid has been shown by Laidlaw to resemble hydrastinine in action. The effects of the three original alkaloids, hydrastine, narcotine, and laudanosine, in the body also present many similarities.

Action.—Hydrastine causes in frogs an increase in the reflex irritability and eventually tetanus exactly resembling that produced by strychnine and like it terminating finally in paralysis.

In mammals the pulse is slowed by comparatively small quantities, while somewhat larger doses cause general feebleness, tremor, dyspnea, and incoördination in the movements. Very large quantities elicit clonic and then tonic convulsions and tetanus, during which the respiration ceases.

Canadine in small quantities produces depression and drowsiness followed by complete recovery without further symptoms. In larger quantities v. Bunge found that it caused a short stage of excitement, which was followed by depression and paralysis of the central nervous system. It has little or no effects on the mammalian circulation when administered in ordinary doses, but very large quantities cause weakness and arrhythmia of the heart. Its injection is followed by violent peristalsis of the intestine and diarrhea.

Hydrastinine differs from hydrastine in causing no marked disturbance of the centers of motion and feeling save in enormous doses, which paralyze the nervous system.

The most important action of hydrastinine is that on the uterus, which increases in tone and often contracts rhythmically and powerfully under its influence. This occurs also in the excised organ and is due to a direct action on the uterine muscle. There is apparently another effect due to stimulation of the ganglia on the fibers of the hypogastric nerves supplying the uterus. This nervous action is not of importance, however, in the pregnant uterus.

Cotarnine differs from hydrastinine in not constricting the vessels or strengthening the heart, so that the blood-pressure falls under it. The action on the uterus also seems rather weaker. The base obtained from laudanosine resembles hydrastinine exactly in action.

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6. Aspidosperma or Quebracho Alkaloids

The bark of Quebracho blanco (Aspidosperma quebracho) contains a number of alkaloids which are probably very similar in chemical composition and which seem to possess almost the same action. They are *Aspidospermine, Aspidospermatine, Aspidosamine, Hypoquebrachine, Quebrachine,* and *Quebrachamine.* Another species of Aspidosperma, Payta, contains two alkaloids, *Paytine* and *Paytanine,* of which Paytine resembles closely the Quebracho alkaloids in its pharmacological action. Quebrachine, or Yohimbine, is also found in the bark of the Yohimbehe tree (Corynanthe yohimbi).

The symptoms produced by these alkaloids are generally ascribed to a direct action on the central nervous system, which is first stimulated and then depressed. The chief seat of action seems to be the medullary centers and the spinal cord, although the basal ganglia may also be more or less involved.

Even small quantities of quebrachine dilate the vessels of the skin and genital organs from action on the vessel walls (Müller). This causes erection and promotes sexual desire in both male and female animals, and this has led to the use of quebrachine (under the name of yohimbine) in veterinary medicine and also in man to improve sexual power in cases of neurasthenic impotence and similar conditions.

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7. Phlorhizin

Phlorhizin (or phloridzin) is not used in therapeutics but has been widely used experimentally in the study of carbohydrate metabolism and may therefore be mentioned briefly. It is a glucoside ($C_{21}H_{24}O_{10}$-$2H_2O$) found in the rootbark of the apple, pear, cherry, and plum trees. When given in large quantities by the mouth it sometimes causes some diarrhea in animals, but apart from this its only effect is glycosuria, which also follows its injection subcutaneously or intravenously. The urine is found to contain 5 to 15 per cent or even more of sugar, sometimes along with acetone and oxybutyric acid, so that the intoxication seems at first sight to resemble diabetes mellitus in man very closely. Phlorhizin induces the same results in man, and the glycosuria is generally not accompanied by any other symptom. It differs from true diabetes, however, in the fact that the sugar of the blood is not increased in amount. The glycosuria is not due to any change in the general metabolism of the body, therefore, but to some alteration of the renal epithelium, by which the blood sugar escapes into the urine instead of being retained in the body and used as a source of energy. This has been definitely proven by Zuntz, who showed that when phlorhizin was injected into one renal artery, the urine secreted by the corresponding kidney contained sugar, while that from the other remained normal for some time. As the available sugar is drained off in the urine, the tissues rapidly manufacture more and pour it into the blood. As long as

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sufficient food is given, the loss of sugar does not seem to entail any increase in the destruction of the tissue protein, but when phlorhizin is given to starving dogs, the waste of sugar has to be made up from the tissues, and the nitrogen of the urine accordingly rises in amount, while at the same time the liver cells become infiltrated with fat globules.

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II. POISONS WHICH INCREASE METABOLISM

1. Dinitrophenol

During the first World War munition workers suffered from poisoning due to dinitrophenol, in many cases the poisoning being severe and even fatal. Experiments upon animals showed that the oxygen consumption was increased many times and that the site of the action of the drug was peripheral rather than central. In 1933 Tainter, Cutting, and their co-workers published the first of their papers upon the subject, confirming the earlier work and suggesting that the drug might prove useful as a stimulant to metabolism and especially as a remedy to be used in obesity.

Administered to man in doses of from 3 to 5 mg. per kilogram of body weight, dinitrophenol increases the metabolic rate from 20 to 30 per cent and this increase may last for from two to three days before it has returned to the normal level. Slightly larger doses cause profuse sweating while doses of 10 mg. per kilogram, in addition to the sweating, cause an increase in body temperature of 3 or more degrees Centigrade. There is a marked increase in respiration and a sensation of great heat.

Toxic doses are followed by nausea and gastro-intestinal distress, sensations of heat, flushed skin, marked sweating, restlessness, rapid and deep respirations and fever. As the fever increases the breathing becomes exceedingly rapid and of maximum depth until the patient is using all his accessory muscles of respiration in an effort to secure adequate aeration. There may be pain in the chest or anginal cramps. The respiration finally fails to keep up with the oxygen consumption, the blood becomes cyanotic and anoxemia develops. There is an increase in lactic acid in the muscles associated with the high fever of over 110° F. Heat rigor of the muscles rapidly follows, starting in the extremities and spreading to the respiratory muscles.

Numerous cases of idiosyncrasy to the drug have been reported, the most common symptom being a pruritic skin eruption. The rash is usually preceded by itching which may become very intense, forming a very disagreeable complication as it leads to excessive scratching. The rash may be of the maculopapular or urticarial type.

The nervous system is affected, as shown by loss of sense of taste, and less frequently, of smell and some disturbance of hearing together with polyneuritis affecting especially the feet and legs. In some cases, the blood-forming organs have been affected, as shown by agranulocytosis which has resulted in death.

One of the most important among the toxic effects which have followed the use of dinitrophenol is the appearance of changes in the lens with the formation of cataracts leading to impairment of vision and even to blindness. These changes in the eye have been encountered in a number of young women who

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have taken the drug in order to reduce their weight. It would seem that the cataract formation is the result of a direct toxic effect of the drug.

Postmortem changes in acute cases have shown marked rigor mortis, acute pulmonary congestion and edema, hemorrhages in the endocardium, pericardium and pia and mild necrotic changes in the kidneys.

The increase in metabolism produced by dinitrophenol differs fundamentally from that following the use of thyroid preparations in which there is a very characteristic increase in nitrogen excretion associated with the increase in metabolism.

Therapeutic Uses.—Dinitrophenol was for a time used for the treatment of obesity. However, the drug is dangerous as shown by the numerous cases of poisoning reported in the literature and by the deaths which have resulted from its administration. It has no place in therapeutics.

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2. Tetrahydronaphthylamine

A poison may be mentioned here which has the property of causing fever temperature and even proves fatal from hyperthermia in some cases. Tetrahydro-β-naphthylamine ($C_{10}H_{11}NH_2$) raises the temperature by increasing the heat production through muscular movement and by limiting the heat loss through constriction of the vessels of the skin and superficial tissues. The muscular movement arises from central nervous excitation, and is shown in tremor and convulsions after large doses; the oxygen absorption and the carbon dioxide production are greatly augmented. The constriction of the cutaneous vessels is also mainly due to stimulation of the vasomotor center, though there may be some slight action on the vessel walls also. The pupil is widely dilated and the eyeball is protruded, from stimulation of the sympathetic mechanism, partly in the periphery but mainly in the central nervous system.

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III. POISONS WHICH ACT ON THE BLOOD

1. Nitrobenzol Compounds

The nitrobenzol bodies are chiefly of interest because they have often given rise to poisoning from their use as explosives, in chemical manufactures, and to flavor alcoholic liquors. They are readily absorbed from the skin and serious symptoms have followed the wearing of clothing dyed with them. In man nitrobenzol causes a grayish-blue, cyanotic color of the skin and visible mucous membranes, often with nausea, vomiting, great muscular weakness, marked dyspnea, delirium, and some convulsive movements of the face and jaws, less frequently of the whole body. Total unconsciousness and coma are followed by arrest of the respiration.

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These effects are due in part to changes in the blood, in part to central nervous action, in which stimulation and paralysis seem to follow one another. The blood is found of a chocolate-brown color, and some of the red cells are either deformed or entirely destroyed. Examined with the spectroscope, methemoglobin is very often found in it, while in other cases an absorption line is observed between the yellow and the red, which does not seem to correspond to that of any of the ordinary hemoglobin products, and has therefore been called the nitrobenzol-hemoglobin line. The blood contains a much smaller amount of oxygen than normally, and artificial respiration or even shaking the blood in air fails to oxidize it further, as the combination of nitrobenzol and hemoglobin seems to be incapable of absorbing oxygen. Similar changes may be produced in venous blood outside the body by shaking it with nitrobenzol. These changes in the blood are the cause of the cyanosis, and the imperfect oxidation of the tissues leads to the appearance of a number of abnormal products in the urine, such as hematoporphyrin. In animals a gastro-intestinal catarrh is almost constantly produced unless the intoxication is very acute, and this occurs even when the poison is inhaled or injected subcutaneously.

Metadinitrobenzol ($C_6H_4(NO_2)_2$) has repeatedly given rise to poisoning in the manufacture of explosives. In action it resembles nitrobenzol, but is more poisonous, and the gastric symptoms are more marked. Amblyopia and jaundice-like coloration of the skin often occur from prolonged exposure to this poison.

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2. Toluylendiamine

Toluylendiamine ($C_6H_3CH_3(NH_2)_2$) has never been used in therapeutics, but it is of importance from the light which it has thrown on some forms of jaundice. Stadelmann found that its administration in dogs produced the typical symptoms of icterus, while in cats the icterus was less marked, but very large quantities of hemoglobin were excreted in the urine. The explanation of this action is the destruction of the red cells in the blood, which leads in the dog to the formation of large amounts of bile pigments in the liver. Some of this pigment is reabsorbed from the bile vessels and leads to typical jaundice. The absorption is promoted by a curious increase in the mucus secretion of the bile ducts, which renders the bile more viscous, and by thus delaying its evacuation into the intestine favors its absorption into the blood. This increased mucus formation is believed to be due to the action of the poison on the secretory cells of the larger bile ducts. The formation of bile pigment from hemoglobin liberates large quantities of iron, which seem to be stored in the liver, spleen, and bone marrow.

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3. Benzol

Benzol, or benzene, is much less poisonous than its hydroxyl compounds, but may give rise to symptoms resembling those of phenol when it is inhaled in large quantities. It was at one time suggested as a general anesthetic, but the preliminary excitement is much greater than that seen in the use of chloroform or ether and partakes more of a convulsive character. Even after unconsciousness and anesthesia are attained, the characteristic muscular tremor of the aromatic compounds continues. In some animals it produces violent and prolonged convulsions, with only partial loss of sensation, and even large quan-

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tities do not cause the complete relaxation of the muscles requisite for surgical operation. It seems to have little or no irritant action on the alimentary tract or kidneys in animals, and is excreted in part by the kidneys as phenol double sulfate, in part unchanged by the lungs.

Hemorrhages occur very frequently in fatal poisoning in man and in experiments on rabbits as a result of fatty degeneration of the arterial walls. A number of cases of fatal intoxication are on record, some of them arising from the drug being swallowed by suicides, but most of them from the accidental inhalation of large quantities in industry. The maximum permissible benzene concentration is now accepted as 1 part per 10,000 when the duration of exposure does not exceed eight hours daily. In acute poisoning the symptoms resemble those of inebriation. In more severe poisoning muscle twitchings, convulsions, paralysis and coma supervene. Death may occur suddenly from cerebral and pulmonary edema.

In chronic benzol poisoning there is disturbance of hematopoiesis with aplastic lesions in the bone marrow. Leukopenia is common but leucocytosis and even **leukemia** may occur. In fact there is suggestive evidence that benzene poisoning may initiate leukemia. The marked fall in the number of the leucocytes of the blood which occurs in benzol poisoning suggested its use in some forms of leukemia. It is, however, not used for this purpose, since better results are obtained by irradiation or by the injection of **radioactive phosphorus.** In polycythemia in which there is an abnormal number of red blood cells, radioactive phosphorus is also preferred to **phenylhydrazine** which was previously used in this disorder.

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IV. HYDROCYANIC OR PRUSSIC ACID

Prussic, or hydrocyanic, acid differs entirely from the other acids in its pharmacological action, and has therefore to be described apart from them.

The pure acid is scarcely ever seen save in the chemical laboratory, and is dangerous to handle, as it is very volatile and when inhaled may produce death within a few seconds. It is generally met with in a very dilute solution, which is formed by the decomposition of one of its salts.

In nature, prussic acid occurs in the secretion of some of the myriapoda, and in the decomposition products of a few glucosides, of which *Amygdalin* is the best known. Amygdalin is in itself practically inactive, but may be decomposed by dilute acids or by a ferment, emulsin, which is generally found associated with it in plants. Prussic acid may be formed from the amygdalin of the bitter almond and the kernels of such fruits as the apple, cherry, plum, etc., and from the bark and leaves of several trees including the laurel (Prunus laurocerasus). A paste formed from bitter almonds has given rise to symptoms from the prussic acid, but a more dangerous substance is the oil of bitter almonds, which consists of benzaldehyde and prussic acid in a loose combination and in very varying proportions. Sweet almonds contain no amygdalin and are therefore harmless. Laurel water and the preparations of Virginian cherry bark contain benzaldehyde and prussic acid in too small quantity to have any poisonous action. Several plants which contain glucosides similar to amygdalin have given rise to poisoning in cattle, probably from prussic acid being freed from the glucosides in the intestine.

Prussic acid and its salts have practically the same action, although none of the latter are so poisonous as the free acid. Cyanogen, $(CN)_2$, also resembles prussic acid in its effects, but is not so active.

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The ferrocyanides and other double cyanides are in most cases harmless but other compounds, from which prussic acid is formed in the organism, are poisonous. The organic combinations containing the —CN radical form two series, the *Nitriles*, in which the nitrogen is trivalent (*e. g.*, $CH_3—C\equiv N$), and the *Isonitriles*, or *Carbylamines*, in which the alkyl is attached to the nitrogen (*e. g.*, $CH_3—N\equiv C$). These compounds are all much less poisonous than prussic acid, and the chief symptoms caused by them arise from gastro-intestinal irritation. The isonitriles are more poisonous than the nitriles and resemble the acid more closely in their action. Both nitriles and isonitriles give rise to the formation of prussic acid in the tissues.

Symptoms and Action.—Prussic acid acts upon almost all forms of living matter; in mammals the central nervous system is especially susceptible. The fatal dose in man is believed to be about 0.05 to 0.08 gram (1–1½ gr.) of the pure acid, so that it is less poisonous than some of the alkaloids and glucosides. It acts so rapidly, however, that it must be regarded as a most dangerous poison. One volume of prussic acid in 2,000 of air is generally fatal to animals.

After very large doses in mammals, there may be practically no symptoms; the animal falls to the ground with a slight convulsive movement or a scream, and death follows in a few seconds from simultaneous arrest of the heart and respiration.

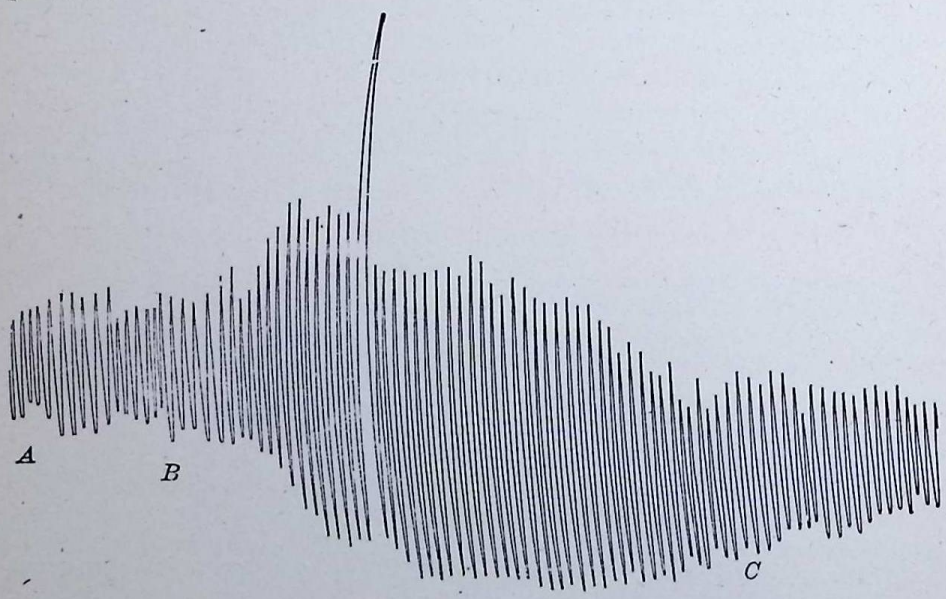

FIG. 69.—Tracing of the movements of the diaphragm (respiration) of the rabbit under a large but not fatal dose of cyanide of potassium injected intravenously. *A–B*, normal respiration. At *B* 1 mg. injected; the respiratory movements are much larger. At *C* recovery. Note the short duration of the stimulation.

In smaller quantities prussic acid has a bitter, acrid, burning taste, which induces salivation, and is followed by numbness in the mouth and throat. A sensation of warmth in the stomach is followed by nausea and vomiting, confusion and headache, dyspnea, slow pulse, and general muscular weakness. The pupils are widely dilated and the eyeballs protrude, as generally occurs in asphyxia. Unconsciousness follows, and then violent convulsions, which pass into paralysis, with involuntary evacuation of the contents of the bladder and bowels; the respiration becomes extremely slow and eventually ceases, while the heart continues to beat for some time afterward.

The **Central Nervous System** is first stimulated and then paralyzed; the convulsions resemble those produced by stimulation of the hind-brain, although the subsequent paralysis seems to include all parts of the central axis.

Striated and unstriated **Muscles** and the **Nerves** are weakened and eventually paralyzed when suspended in an atmosphere of the gas, but they are not affected

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in poisoning; the nerves are more readily poisoned than the muscles. When prussic acid in solution is applied locally to the **Skin** it produces numbness and partial loss of sensation, but this does not follow in general poisoning.

The **Respiration** is rendered quicker and deeper by the injection or inhalation of small quantities of prussic acid. After larger quantities, the acceleration is often interrupted by a prolonged pause after which the breathing returns spontaneously. In fatal poisoning no such return occurs, and after very large doses the breathing may cease within a few seconds.

Metabolism.—Cyanide exercises a depressant action on protoplasm in general. Both plants and animals are retarded in their movements and in their nutritive processes by its presence, although they may recover and show no subsequent deterioration, provided the poison acts only during a short time and in sufficient dilution. This action of cyanide is due to the fact that it retards the normal respiration of the cell. In consequence of this, the oxyhemoglobin of the blood is not reduced in the capillaries, so that the venous blood has the same bright red color as the arterial. Prussic acid is rapidly changed to harmless products in the tissues, however, provided a lethal dose has not been given, and as this process goes on, the protoplasm recovers its oxygen-absorbing power, the expired air becomes less rich in oxygen and richer in carbon dioxide, and the venous blood assumes its ordinary dark color. The usual results of imperfect oxidation in the tissues are seen in an increase in the sugar and lactic acid in the blood, and augmented nitrogen, urea and unoxidized sulfur in the urine, although the last substance may be accounted for by the thiocyanate formed.

This lessened O_2 absorption in the tissues arises from the intracellular ferments being paralyzed in animals in the same way as in plants. In fact the whole action of prussic acid is so like that of asphyxia, that there is every reason to hold that it is limited to this arrest of oxidation

Prussic acid is changed, in part, to thiocyanate in the tissues and excreted in this form in the urine, while part of it undergoes further and unknown changes.

If normal blood is brought in contact with a solution of peroxide of hydrogen, it effervesces, owing to the liberation of oxygen by the peroxidase ferment, and the peroxide, being all decomposed in this way, the oxyhemoglobin remains unchanged; if, however, prussic acid be present, no effervescence occurs, because the peroxidase is rendered inert, and the hemoglobin is at once changed to methemoglobin from the oxidizing action of the peroxide, which is no longer dissipated.

Therapeutic Uses.—Sodium cyanide has been injected intravenously in the form of sodium cyanide as a respiratory stimulant (Loewenhart), and although a most effective agent for this purpose the lethal activity of the drug has militated against its adoption therapeutically.

Treatment of Cyanide Poisoning.—The combination of sodium nitrite and sodium thiosulfate is used in the treatment of cyanide poisoning. In dogs, this combination is capable of detoxifying about 20 doses of sodium cyanide even after respiration has stopped, as long as the heart is still beating. Sodium nitrite alone will detoxify about four lethal doses; the thiosulfate about three. When used together, there is a potentiation of the action which depends upon the formation of methem-

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oglobin by sodium nitrite. The latter removes the cyanide ions from the tissues and couples with them to form cyanmethemoglobin which is relatively non-toxic. The sodium thiosulfate in turn converts cyanide to thiocyanate by means of an enzyme called rhodanase. In the treatment of a victim of cyanide poisoning, pearls of amyl nitrite are administered while sodium nitrite and sodium thiosulfate solutions are being prepared. Ten cc. of a 3 per cent solution of sodium nitrite are injected at the rate of $2\frac{1}{2}$ to 5 cc. per minute, followed by 50 cc. of a 25 per cent solution of sodium thiosulfate. At times the poisoning reappears; in which case the treatment is repeated in half of its previous dose (Chen).

Methylene blue has also been suggested as a clinical antidote in cyanide poisoning. The mechanism of the antidotal action of methylene blue has been ascribed to the formation of methemoglobin which in turn binds the cyanide as the stable non-toxic cyanmethemoglobin. From this compound the cyanide is freed so gradually that it can be detoxicated by normal body processes.

Preparations

Acidum Hydrocyanicum Dilutum (B. P.), a 2 per cent solution formed from potassium ferrocyanide or silver cyanide. It is a colorless fluid with a characteristic smell and taste, and ought not to be kept long, as it is liable to decomposition; much of that actually used in medicine is partially decomposed and therefore under 2 per cent in strength. Dose, 0.12 to 0.3 mil.

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N. COLCHICUM

Colchicine and *colchiceine* are two nearly related bodies found in the seeds and corm of Colchicum autumnale, which owes its activity to their presence. Colchicine is the methyl ester of colchiceine, which is much less active pharmacologically. Colchicine is feebly basic, while colchiceine is slightly acid in reaction.

Symptoms.—No symptoms whatever follow the use of colchicum in small quantities. Large doses, corresponding to 4 to 5 mg. of colchicine, cause diarrhea with some griping in susceptible persons, and in the therapeutic use of the drug purging is often observed; symptoms only arise several hours after the drug is administered, and this interval is not shortened by increasing the dose.

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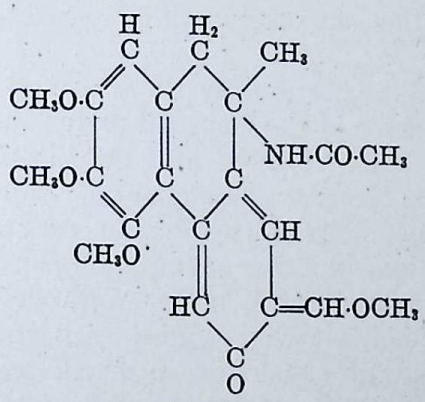
In poisoning with colchicine, whether given by the mouth or injected hypodermically, the symptoms arise from the alimentary tract. Pain in the gastric region is followed by salivation, nausea, vomiting, and diarrhea. At first the evacuations are the ordinary contents of the stomach and intestine, but afterwards a quantity of sticky mucous fluid may be ejected, often streaked with blood. Later, a condition of depression, apathy, and collapse follows, and the movements become slow and difficult, more especially in the posterior extremities, which eventually become completely motionless; the paralysis then progresses upward until the movements of the fore-limbs and respiratory muscles are involved, when death occurs from asphyxia. In man the intelligence remains until death, though there is generally some giddiness and precordial anxiety and occasionally some confusion or even delirium preceding the collapse.



Colchicine

In mammals poisoned with colchicine the alimentary canal exhibits all the appearances of acute gastro-enteritis, with numerous ecchymoses, especially in the upper part of the bowel. In less acute cases these inflammatory symptoms are less marked, and in man there is seldom more than catarrh of the duodenum.

The **Circulation** is apparently but little affected. In animals, the blood-pressure and heart rhythm remain normal, and though a small, rapid pulse may be one of the features of the poisoning in man, this is due to the collapse rather than to any direct action on the circulatory organs.

The **Respiration** is slow, but is deep and full at first. Later it becomes shallow, and the failure of the center is the cause of death, the heart continuing to beat for some time afterwards.

The **Movements of the Bowel** are much hastened when the symptoms set in, and Dixon states that colchicine acts on the bowel in the same way as pilocarpine, and that its action is antagonized by atropine; but this is entirely inadequate to explain the acute inflammatory appearances, which are evidently due to an irritant action on the mucous membrane. Increased movement is said to be induced in the plain muscle of the spleen, uterus, and bronchial muscle from a pilocarpine-like action.

When **Applied Locally** to sensitive mucous membranes, or when

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injected hypodermically, colchicine is intensely irritating, producing redness and prickling in the skin, and a burning sensation in the mouth and throat.

The **Nervous Symptoms** are supposed by some to be due to a direct action on the central nervous system, but are to be ascribed rather to a condition of collapse produced indirectly through the action on the abdominal organs.

The influence of colchicine on the **Kidneys** varies, for in some cases complete anuria is produced for many hours, while in others the urine is slightly increased. The constituents of the urine are not materially altered by ordinary therapeutic doses of colchicum, and, in particular, the uric acid shows no constant change in amount. In animals, bloody urine is sometimes passed after colchicine.

In poisoning with colchicine the leucocytes are at first reduced in the peripheral circulation, but afterwards increased to beyond the normal numb r.

All of these symptoms are exactly those caused by a large number of poisons, including some of the bacterial toxins and the heavy metals. Many local irritants when injected into the blood or when absorbed from the subcutaneous tissue or the alimentary canal exercise an immediate, local action, which betrays itself in pain or ecchymosis and swelling at the point of injection, but these symptoms pass off in a short time, and the animal becomes apparently normal for many hours or even days. At the end of this time, however, symptoms begin to develop at two points—in the alimentary canal and in the kidneys—with irritation and later acute inflammation at these points. At first the irritation excites only diarrhea and diuresis, but as it goes on, gastro-enteritis and anuria or hematuria may be produced. The symptoms from the intestine and kidney may not be equally well marked; at one time the one becomes inflamed while the other is only subjected to mild stimulation, while at other times both are the seat of acute inflammation. The inflammation of the bowel produces a condition of collapse, which is seen also in various intestinal diseases, such as cholera.

It has been shown recently that colchicine exerts a remarkable effect upon the mitosis of cells in both normal and malignant tissues. This action, which was first described by Dustin, consists in a great increase in mitotic figures, a condition which is best seen in tissues where cell division is of frequent occurrence. Large numbers of abnormal mitotic figures appear, and the chromosomes may be scattered and clumped into groups. Inhibition of the normal process of mitosis has taken place in the metaphase in that there is not a vestige of spindle mechanism visible and very few cells showing the later stages are to be seen. The number of mitotic figures in an area may increase from a normal of 2 or 3 up to 10 or 12 in a few hours, with perhaps 50 per cent of the cells showing mitosis in twelve hours. The abnormality is due to the failure of the mechanism of which the spindle is the visible attribute (Ludford), the dividing cells accumulating in metaphase as a result of the inhibiting effect of the drug on the completion of mitotic division.

On account of this effect of colchicine it has been used as an index of the rate of cell growth. Thus by simultaneous injection of colchicine and estrogenic hormone in the rat and examination of the tissues at intervals thereafter it is possible to follow the action of the estrogen by noting the site at which mitotic figures accumulate.

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Colchicine has been used in horticulature to modify the genetic pattern and thus induce polyploidy and mutations in plants. It has also been used in attempting to modify the growth of cancerous tissue (Levine).

Therapeutic Uses.—Colchicum has long been used in gout on purely empirical grounds. In acute cases of gout colchicine is administered in 0.5 mg. tablets or in the form of the tincture of colchicum in doses of 1 to 2 cc. (20 to 30 minims) every four hours until there is some evidence of its action, such as nausea or slight purging. Prolonged administration is not advisable. The pathology of gout is so obscure that no rational treatment for it can be looked for at the present day, and the efficacy of colchicum in this disease can, therefore, be argued solely from clinical experience. There is no doubt that the pain and inflammation around the joint in an acute attack of gout are relieved by colchicum, often without any other obvious effect, but sometimes only after enough has been given to cause some diarrhea. In the intervals between the acute attacks, colchicum does not appear to have any beneficial effect, but by taking the drug at the first indication of an impending attack it is possible to ward it off in some cases. The uric acid excretion is not altered by colchicum treatment in gout, nor in health.

PREPARATIONS

U. S. P.

COLCHICI SEMEN, colchicum seed, the dried ripe seeds of *Colchicum autumnale*, containing not less than 0.45 per cent of colchicine.

TINCTURA COLCHICI SEMINIS, tincture of colchicum seed. Dose, 2 cc.

COLCHICINA, colchicine, an alkaloid obtained from colchicum. Dose, 0.5 mg.

TABELLÆ COLCHICINÆ, colchicine tablets. Dose, 0.5 mg.

B. P.

COLCHICI CORMUS, colchicum corm. Dose, 0.12 to 0.3 gram.

EXTRACTUM COLCHICI SICCUM. Dose, 0.015 to 0.06 gram.

COLCHICI SEMEN. Dose, 0.12 to 0.3 gram.

EXTRACTUM COLCHICI LIQUIDUM. Dose, 0.12 to 0.3 mil.

EXTRACTUM COLCHICI CORMI LIQUIDUM, liquid extract of colchicum corm. Dose, 0.12 to 0.3 mil.

TINCTURA COLCHICI. Dose, 0.3 to 1 mil.

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O. CINCHOPHEN AND ITS DERIVATIVES

A number of compounds of the type of quinoline carboxylic acid were discovered by Nicolaier in 1908 to increase the amount of uric acid excreted in the urine in a remarkable way; among these, phenylquinoline

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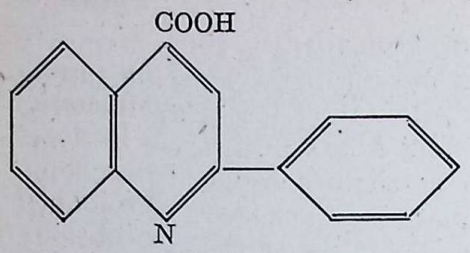
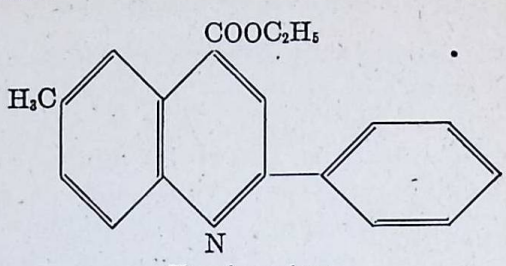
carboxylic acid was the most efficient and was introduced into medicine under the name of *cinchophen* or *atophan*.



Cinchophen



Neocincophen

A nearly related substance, the ethyl ester of methylcinchophen is employed under the name of *Neocinchophen* or *Novatophan*. Because of its lesser toxicity this derivative has replaced cinchophen in therapeutics.

Cinchophen may be taken in large quantities (6 grams) without any obvious symptoms, but considerably smaller doses (2 grams) may suffice to increase the uric acid of the urine threefold; in other cases the augmentation is not so great, but it is increased in the majority of instances from 40 to 50 per cent. The urine is little changed in amount but is often turbid when passed, and deposits quantities of urates on standing; this turbidity may appear within forty-five minutes of the administration of cinchophen. This increased elimination of urates and uric acid occurs in persons on ordinary diet and also on a purine-free diet, in which the uric acid excreted can arise only from the tissues. When cinchophen is given for one day only, the excretion of uric acid rises immediately, and the following day it sinks below the normal amount, and this depression of excretion may continue for even three days as if the first large excretion had exhausted the supply. When it is given continuously for some time, the excretion falls rapidly after the first day and may reach the normal or even below it on subsequent days; very often, however, more uric acid is excreted each day than normally, although the marked excretion attained at first is not repeated.

The more rapid excretion of uric acid is sometimes, but not always, attended by a fall in the uric acid content of the blood. In many cases the blood uric acid has been found to be above normal even when there is an increased excretion through the urine. The action has been ascribed to a direct effect on the kidney, rendering it more readily permeable by the urates, so that those previously retained in the blood through the difficulty attending their elimination by the kidney now escape in the urine. The rapid removal of the urates of the blood and tissues appears often to increase the formation of uric acid in the body, for the continued treatment with cinchophen is attended by an abnormally large amount of uric acid in the urine even when it extends to weeks in duration. The evidence points to cinchophen increasing elimination by the kidney; probably the normal reabsorption of urates in the tubules being hindered by cinchophen. In addition, there is doubtless an additional action upon the tissues, as shown by the fact that even with an increased output of uric acid there may still be an abnormally high percentage

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in the blood. Cinchophen appears to undergo decomposition in the tissues for the most part, though some appears in the urine unchanged. Like so many other aromatic substances, cinchophen reduces fever temperature and lessens pain (see Antipyretic group).

Grabfield and Gray found that in dogs the administration of cinchophen was followed by an increase in the total nitrogen, sulfur, allantoin and uric acid in the urine, the effect on the nitrogen being brought about through a direct action on the kidney similar to that of the salicylates where the relationship of the sulfur excretion to the nitrogen excretion remains essentially constant. Denervation of the kidneys in dogs reversed the action of cinchophen upon the uric acid excretion, there being a very marked lessening in the output. Ergotamine also eliminates the increase in uric acid while atropine does not affect it, so that it would appear that the action of cinchophen upon uric acid excretion in the dog is through the adrenergic fibers. As the increase in allantoin is not affected by denervation of the kidney but is eliminated by both atropine and ergotamine, Grabfield and his associates conclude that the cinchophen increase in allantoin is through both adrenergic and cholinergic fibers.

Inasmuch as the increased amounts of uric acid which are excreted in the urine under the influence of cinchophen probably come at least in part from stores of uric acid in the tissues, Fürth and Edel studied the effect of cinchophen upon the uric acid content of the liver of rats and they found that very small doses of the drug caused a marked decrease in the uric acid content of the organ, but in no case was there complete disappearance of the product—a residue of 1 to 2 mg. per cent being retained in every instance. The optimum dose for this effect was found to be about 0.8 mg. of cinchophen daily per kilo of body weight or what could correspond to about 0.05 gram for a man of average weight or, in other words, about one-tenth of the average therapeutic dose of the drug. A sufficient dose of cinchophen or of neocinchophen produced a considerable loss of weight but in the production of this change cinchophen was found to be about three times as toxic as its newer ally. Barbour and Gilman gave neocinchophen to young rats in doses equivalent to 1 gram per kilogram of body weight for a period of one hundred days with no effect on weight and no demonstrable change in the liver. An equal amount of cinchophen given under the same conditions caused death in a very few weeks. The dose of neocinchophen necessary for the production of an effect upon the temperature was found to be two and a half times that of cinchophen.

Toxicity.—Poisoning not infrequently occurs following the use of cinchophen. In many cases the symptoms are similar to those usually seen in drug idiosyncrasies, such as various cutaneous disturbances, as pruritus, urticaria and different forms of skin eruptions. Anaphylactoid reactions may occur, or gastro-intestinal disturbances, but more serious than these are the cases of toxic hepatitis with jaundice and, in a considerable number of cases, acute yellow atrophy with death. The special factors or conditions which lead to these cases of serious poisoning are unknown. Long-continued use of the drug has been reported in some instances. In others disturbed kidney function interfering with excretion of the drug may be a factor, but more commonly it is probably due to some previous impairment of the liver rendering it more susceptible to the drug. The hepatic changes are much less common following the use of neocinchophen, but on account of its close relationship to the parent drug it also should be used with discretion.

In a comparative study of the effects of cinchophen, neocinchophen and sodium salicylate upon the livers of dogs and rats, Barbour and Fisk found that

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all three drugs affected the liver, but that cinchophen was by far the most toxic of the three and that neocinchophen had the least effect upon the organ. Upon the kidneys of dogs, sodium salicylate was the most harmful and neocinchophen had the least effect.

Gastric ulcers have been produced experimentally in dogs by a number of workers. It is possible with the continued administration of cinchophen to produce in dogs ulcers having all the appearance of those which are found clinically in man. There is first an acute gastritis involving the fundic portion of the stomach, and this is followed in a week or two with a perforating type of ulcer located on the lesser curvature near the pylorus. There is an increase in quantity of gastric juice but no heightened degree of acidity. If the drug is stopped, the ulcer heals rapidly, recovery being complete in from two to seven weeks (Bollman, Stalker and Mann).

Therapeutic Use.—Neocinchophen is used in **gout**, in which condition it is given in doses of about 0.3 gram (5 gr.) four times a day. When large doses are given, it is advised to keep the urine alkaline by the use of sodium bicarbonate or potassium acetate or citrate. In gout, neocinchophen increases the uric acid elimination in the same way as in health and does not usually induce any other symptoms. This free removal of uric acid appears to be of benefit in the disease, and several observers state that the deposits of urates (tophi) are lessened in size and the chronic inflammation of the joints is relieved; others have observed less benefit and deny that uric acid deposits are reabsorbed.

In acute articular **rheumatism** neocinchophen has also proved to be quite efficient. Long-continued use of the drug is to be avoided on account of the danger of poisoning.

Preparations

U. S. P.

Neocinchophenum, neocinchophen, a white to pale yellow crystalline powder practically insoluble in water. Dose, 0.3 gram.

Tabellæ Neocinchopheni, neocinchophen tablets. Dose, 0.3 gram.

B. P.

Cinchophenum, cinchophen. Dose, 0.3 to 0.6 gram.

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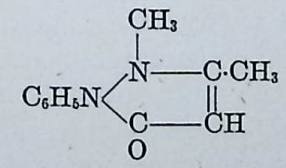
P. THE ANTIPYRETICS. (ACETANILIDE AND ANTIPYRINE SERIES)

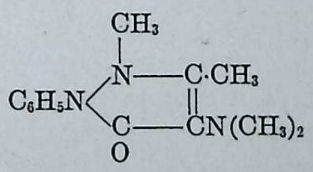
Up to 1875 the only means of combating high temperature were baths, vegetable alkaloids, such as quinine, or alcoholic preparations, but in that year Buss discovered that salicylic acid produces a fall in the fever temperature, and soon afterward carbolic acid and resorcin and its isomers were employed as antipyretics. A very large number of antipyretics have been introduced since that time, but most of them have had only a temporary vogue, and those in general use at the present time are comparatively few in number.

Quinine and quinoline, as well as some of the simpler compounds, were among the earlier antipyretics suggested. *Quinoline* (C_9H_7N) was soon found to be dangerous from its producing collapse, but its derivatives, *Kairine* ($C_9H_9(OH)$-$N—C_2H_5$); *Kairoline* ($C_9H_8(CH_3)(OH)NH$), *Thalline* ($C_9H_9(OCH_3)NH$) and Analgen, were used extensively, although they have now been entirely abandoned.

Chemistry.—The antipyretic, introduced in 1884 under the name of **Antipyrine** or Phenazone, which is derived from phenylhydrazine, proved superior to all of the earlier drugs. **Phenylhydrazine** ($C_6H_5—NH—NH_2$) itself also produces a fall in the fever temperature, but this is frequently accompanied by collapse and changes in the blood, which prevent its use in medicine. Several of the simpler compounds have received a more or less extensive trial as antipyretics, but have proved dangerous and inferior to Antipyrine (phenyldimethylpyrazolon) which is still largely used as an antipyretic, either in its original form, in the form of its derivatives, or as a constituent of numerous combinations with various analgesics. Among these may be mentioned **Aminopyrine** or **Pyramidon** (dimethylaminoantipyrine), **Hypnal** (chloral and antipyrine), **Salipyrine** (salicylic acid and antipyrine), etc.



Antipyrine



Aminopyrine or pyramidon

Antipyrine early found a rival in Antifebrine or **Acetanilide**, which was advised as an antipyretic in 1886 by Cahn and Hepp. **Aniline** ($C_6H_5NH_2$), from which it is derived, has also some action on the temperature, but like phenylhydrazine produces dangerous collapse and destruction of the blood cells. Acetanilide ($C_6H_5NHCOCH_3$), the first of its derivatives to be introduced, is not entirely devoid of this poisonous action, and has been supplanted to a considerable extent by more complex and less poisonous bodies. It was soon found that both aniline and

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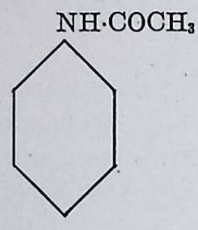
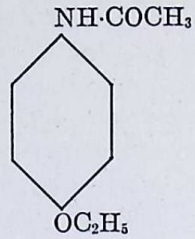
acetanilide undergo a partial oxidation in the body, with the formation of aminophenol or its derivatives, and the belief that the antipyretic effects were due not so much to the original substance as to these oxidation products led to the introduction of numerous derivatives of para-aminophenol ($NH_2—C_6H_4—OH$).



(Acetanilide)



Phenacetine
(Acetophenetidin)

Para-aminophenol has antipyretic properties but suffers under the same disadvantages as aniline. Among its derivatives the most satisfactory antipyretics are those in which the hydrogen of the hydroxyl is substituted by an alkyl group, while an acid radicle is added to the amino-radicle. The first of its compounds to be introduced was **Phenacetine** which differs from acetanilide only in the addition of an ethoxyl group in the para position. It is less dangerous than acetanilide and antipyrine, and has therefore been largely used, and has been followed by other bodies which are identical with it, except for the acid radicle attached to the nitrogen. Among these phenetidines may be mentioned *Lactophenine* (lactyl-phenetidine), *Triphenine* (propionyl-phenetidine), *Malakine* (salicyl-phenetidine), *Citrophen* (citryl-phenetidine), Kryofine (methylglycolic phenetidine), *Phenocoll* (glycocoll-phenetidine), etc.

Many of the antipyretics at present in use probably owe their activity to the formation of simple derivatives of paraminophenol in the tissues, and differ chiefly in the rapidity with which this decomposition occurs; when it is quick, it is followed by destructive blood changes and a tendency to collapse, while the antipyretic effects pass off soon. Those drugs are found the most satisfactory antipyretics in which the decomposition proceeds gradually, so that the temperature falls slowly and remains low for a longer time. The simpler antipyretics, such as acetanilide, have given way largely therefore to the phenetidine compounds. Among these it is impossible to determine the most suitable, but none of them has been proved to be superior to phenacetine. Where the merits seem so equally divided, it is perhaps more important to learn to use one with judgment than to hurry after each new product without sufficient experience with its predecessor.

Symptoms.—The effects of the antipyretics vary not only with the dose but with the individual patient. Many persons can take very large doses without apparent effect, while in others comparatively minute quantities produce symptoms of greater or lesser importance. The effects are not always the same, even in one individual under the same dose of the antipyretic, and it is impossible to state at present what are the conditions that involve the peculiar train of symptoms. A very

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large number of disorders have been attributed to the antipyretics in man, but it is impossible to consider any here except those more commonly observed. Among these are *skin eruptions* of various forms, such as red, erythematous, itching patches or more widely diffused hyperemia resembling the onset of measles or scarlatina; urticaria occurs not uncommonly, while eczema and bullæ are rarer. In some cases an edematous swelling has been observed. Some *fever* occasionally accompanies the eruption and renders the diagnosis from the infectious exanthemata even more difficult. These skin affections seem to be elicited more frequently by antipyrine than by acetanilide and the phenetidine compounds. The skin eruption resulting from the use of antipyrine is frequently clinically identical with that which sometimes follows the use of phenolphthalein (see page 236). Profuse *perspiration* not infrequently follows the use of the antipyretics in fever, and if the fall in temperature is rapid, and the action of the drug passes off soon, the subsequent rise of temperature may be accompanied by *shivering and rigor*, but these symptoms are scarcely to be looked upon as direct effects of the drug, but rather as resulting from the rapid changes in temperature. They are produced much more frequently by the older and simpler antipyretics than by those of more recent introduction.

Sometimes *catarrh*, burning and swelling *of the throat* and *mouth* are observed after antipyrine, and more rarely *nausea* and *vomiting*. *Cerebral symptoms* are rarely elicited beyond slight dulness, confusion, or apathy. Alterations of the hearing similar to those described under quinine have been observed in some cases. More serious symptoms are those of *collapse*, which are sometimes induced by acetanilide. In the milder cases the skin is cool, the pulse is rather small and rapid, and some anxiety and alarm are felt by the patient, but the condition passes off in short time. In more severe cases the skin is cold and covered by a clammy perspiration, the heart is weak, irregular and sometimes fluttering, the temperature may be subnormal and the pupils are slightly dilated. The patient may be conscious, fainting may occur, or an apathetic, confused condition may be produced. The weakness of the heart is the chief source of anxiety, and the total failure of the circulation seems to be the cause of death. These cases of collapse occur more frequently when a rapid fall of temperature has been produced than under other circumstances, but may be observed in cases in which no fever has been present.

Marked **cyanosis** occurs sometimes under acetanilide and the earlier members of the series, very rarely under antipyrine and the phenetidine compounds. It arises from the formation of methemoglobin in the blood, and when this is accompanied by collapse, the cyanosis may be very intense. It is often accompanied by dyspnea and acceleration of the pulse, and it lasts for a varying length of time, sometimes passing off in a few hours, at other times persisting for several days.

Occasionally a certain **tolerance** is gained, and larger doses of the antipyretics are required to produce effects than were necessary at the beginning of the treatment. Many cases of **chronic poisoning** are recorded from the habitual use of acetanilide. The symptoms con-

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sist in disturbance of the digestion, cyanosis, tremor, muscular weakness and general mental debility; the blood is often chocolate-colored from the formation of methemoglobin, and the urine often contains hemoglobin or its products, or may be colored by the oxidation products of paraminophenol. The condition is sometimes difficult to recognize, especially as the patient may deny that the drug has been taken. The symptoms disappear rapidly when it is given up.

These drugs are by no means very poisonous, normal animals showing no reaction to doses which are sufficient to cause marked changes in fever. In the frog **Antipyrine** causes an increase in the reflex irritability, which sometimes leads to tetanic convulsions and is followed by depression, loss of the voluntary movements, and eventually by complete paralysis and death. In mammals its injection is followed at first by a period of quiet and sometimes of somnolence, which is said by some authors to occur also in the frog previous to the increase in the reflex irritability. Some rise in the reflex irritability may be made out in the mammal at this stage, and large doses cause convulsions and tremors, and subsequently unconsciousness and collapse, ending in complete paralysis. The pulse is accelerated by small doses, while in the later stages of poisoning it may be slow, and some dilatation of the skin vessels and flushing have been observed. The respiration is at first accelerated, and then becomes slow and irregular, when large doses are injected. In dogs vomiting and dilatation of the pupil generally occur.

Acetanilide is more poisonous than antipyrine in both frogs and mammals, but resembles it in its general effects, producing first a more or less marked stage of lessened activity, followed by convulsive movements. The respiration is not so much accelerated as by antipyrine, and, according to some observers, is slow from the beginning of the action. The heart is first accelerated and then slow and irregular, and cyanosis and collapse are more frequently observed than under antipyrine. Feeding experiments in mice and rats indicate a relative low toxicity. There is also some protective action derived by the simultaneous feeding of alkaline salts, for if sodium bicarbonate be added to the acetanilide in the molecular ratio of 2 to 1, the mortality from acetanilide is reduced. The antipyretic action in rats is not altered nor are the blood changes seen in chronic poisoning prevented by the presence of alkali. In chronic feeding experiments there is no evidence of addiction or cumulative effect seen—rather a distinct development of tolerance which is more marked if the animals are subjected to a rapid increase in dosage. **Phenacetine** and its allies are much less poisonous than acetanilide and antipyrine, but in large quantities produce almost identical effects—somnolence followed by convulsions, cyanosis, and collapse. **Lactophenine** is said to have a more sedative effect than the other antipyretics, and to induce complete narcosis in the rabbit.

Agranulocytosis.—In 1922 a new clinical syndrome was described by Schultz and designated as "Agranulocytosis." It was characterized by an ulcerative angina, severe leukopenia, marked prostration and was not infrequently followed by death. On account of the prominence of the anginal symptoms the condition was later designated "Agranulocytic Angina." Schultz suggested that the condition might be due to depression of the bone marrow either by some microörganism or by some chemical agent. It is now recognized that agranulocytosis may occur as a result of depression of the bone marrow in severe infections or as a result of hypersensitivity to a number of drugs, particularly aminopyrine, dinitrophenol, gold salts, organic arsenicals, the sulfonamide derivatives, thiouracil, and toxic chemicals. Because of its widespread use, aminopyrine as a cause of agranulocytosis has received most

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attention. In the vast majority of cases of agranulocytosis there is a history of aminopyrine administration, taken either alone or in combination with one of the barbiturates.

Various explanations have been advanced as to the mechanism involved in the intoxication. It is well known that it is only in the very occasional individual that the drug will produce these effects. In the present state of knowledge it can only be designated as a case of unusual susceptibility or idiosyncrasy to the offending drug. There is a depression of the myelocytic function of the bone marrow resulting in a marked decrease in the granulocytes of the peripheral blood. This deprives the body of its major defensive mechanism, resulting in bacterial invasion of the mucous surfaces: mouth, throat, rectum and vagina. The relation of aminopyrine to certain of the cases has been clearly demonstrated, the administration to convalescent persons of a small dose of aminopyrine being followed by a very rapid reappearance of the granulocytopenia.

The disease is easy to diagnose—the decrease in granulocytes being characteristic. The most important element in the treatment is the avoidance of the offending drug. Blood transfusions have been used, and injections of **pentnucleotide** have been given into the gluteal muscles. The latter drug has been tried in the treatment of these cases on account of the marked increase in the leucocyte count which follows its administration to normal individuals. Its value in agranulocytosis is still a matter of discussion. More recently folic acid and crude liver extracts have also been advocated since in experimental animals the leukopenia which follows the administration of certain drugs (particularly the derivatives of sulfanilamide) has been prevented by the addition of folic acid or crude liver to the diet.

Action.—The action of these drugs on the various organs is very imperfectly understood. The **Nerve Centers** are affected, as is shown by very slight somnolence occasionally seen, but much more frequently by the relief of pain, as in neuralgia and headache; after phenacetine the general sensitiveness of the body may be shown to be lower by measurements of the threshold sensibility of the skin. This is generally attained without any observable depression of mental activity and is, therefore, quite distinct from the analgesia obtained by the use of morphine or anesthetics. This suggests that the antipyretics relieve pain by affecting not the cerebral cortex, but some lower point, which may be assumed to be a synapse on the path conveying pain sensations; there are two of these, one in the spinal cord and one in the thalamus, and as the antipyretic action of this group is due to changes in the neighborhood of the latter, it seems likely that their action in abating pain may be located here also (Head).

Most of the antipyretics increase the excitability of the spinal cord at first, and this may lead to convulsions in the frog. The origin of the convulsions in mammals is still somewhat doubtful; in general, they seem to be of cerebral origin, but when large quantities are injected, they are seen even when the spinal cord is divided from the brain, so that the cord appears to be thrown into a condition resembling that

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discussed under strychnine poisoning. In considering the cause of these convulsions perhaps too little weight has been laid by some writers on the changes in the blood, respiration and circulation, for it is possible that the convulsions in some cases are asphyxial in character and not due to the direct action of the poisons on the brain.

In ordinary poisoning the peripheral **Nerves** and nerve-ends do not seem to be seriously involved, and the final paralysis in both frogs and mammals is undoubtedly central. Santesson found that antipyrine tended to increase the power of the frog's **Muscles**, and several observers have noted that the nerves and motor terminations are paralyzed by the direct application of this drug. Antipyrine has some effect as a local anesthetic when applied to the mucous membranes.

The **Heart** in the frog and mammals is first accelerated and then slowed by the antipyretics in general, these alterations being entirely independent of the inhibitory mechanism and due to a direct effect on the cardiac muscle. The increased rhythm of the heart leads to a slight rise in the blood-pressure, which sinks again as the pulse becomes slower. There is no satisfactory proof that the vasomotor centers are involved in the rise of pressure, although it is not unlikely that they undergo a primary stimulation at the same time as the respiratory center.

Most of this series, except antipyrine and its compounds, tend to cause alterations in the **Red Blood Cells** when they are given in large quantities. This action is manifested especially by the simpler bodies of the series, and is still more marked in poisoning from aniline, phenylhydrazine, paraminophenol or quinoline. On the other hand, most of the phenetidine compounds produce it much more rarely, and antipyrine seems devoid of this action. The alteration consists in the formation of methemoglobin, which may be readily detected by its characteristic spectroscopic appearance. Small quantities of the antipyretics cause its formation within the blood cells, which remain intact, but larger doses, especially of the more poisonous members, destroy the red blood cells and free the methemoglobin in the plasma. In the blood, various distorted, shrunken red cells may be observed, often entirely devoid of coloring matter, while part of the methemoglobin escapes through the kidneys, and nephritis occurs in some cases with albumin, hemoglobin, and even blood in the urine. This effect on the blood arises from the decomposition products of the antipyretics, such as an hydroxylamine product ($C_6H_5NOH.COCH_3$) from acetanilide, and perhaps paraminophenol or the corresponding quinoline derivatives from others; this decomposition proceeds more slowly in phenacetine and its allies and is absent after antipyrine, which explains the rarity of the symptoms after these drugs; it only occurs in the tissues and no methemoglobin is formed when the antipyretics are added to drawn blood.

All of the antipyretics have some **Antiseptic** action, which varies in the different members with their solubility and stability. Antipyrine is found to preserve blood from putrefaction for some days when added to it so as to form a solution of 2 to 5 per cent. Watery solutions of this strength destroy protozoa and stop the movements of the leucocytes.

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The action of the antipyretics on the **Metabolism** of healthy men and animals has been the subject of a number of investigations which have by no means given uniform results, especially in regard to the nitrogen elimination. *Antipyrine* has no influence, or only an insignificant one, on the metabolism of the healthy tissues, whether this is measured by the nitrogenous excretion or by the gaseous exchange in the lungs. *Acetanilide*, on the other hand, has a distinct effect on the nitrogen eliminated, although this is elicited only by large doses. The exchange of gases in the lungs is not affected by the antipyretics in healthy animals, and no definite change has been observed in the excretion of the uric acid.

The specific effects of the antipyretics on the **Temperature**, while recognized by all, have been the subject of endless discussion, owing to the complex mechanism through which they are elicited. In the normal animal the temperature is but little altered, except by doses large enough to produce collapse, but when it is abnormally high, as in fever, the antipyretics cause a fall of greater or less extent. This difference in the reaction of normal and fevered animals has aroused much interest. It may be an example of a general law for which some evidence is available, that it is easier to reduce an abnormal organ or function to its normal condition, than to change a normal one to unusual activity or inactivity; a definite rate of function is the habit of each organ and it moves away from this normal with difficulty and returns to it with readiness. The fall in temperature occurs at varying intervals after the ingestion of the drug, but, except in refractory cases, always begins within two to three hours. Its extent varies, the temperature in some cases reaching the normal or even a subnormal point, while in others the change is insignificant. Continuous fever without any natural rise and fall is much less affected, as a general rule, than one with alternate rise and fall of the temperature, and in the latter form the result is greater if the drug is given at the beginning of one of the natural remissions.

The fall in temperature is often accompanied by flushing of the skin and perspiration. The oxygen absorbed and the carbon dioxide excreted are lessened, and the urea and nitrogen of the urine are also diminished after antipyrine, while they are not infrequently increased after acetanilide, especially when administered in large quantities. The heart is often reduced in rate, and the pulse improves in strength, but these changes are due to the fall in the temperature and not to the direct action of the drugs. Some remedies owe their antipyretic properties to their increasing the secretion of the sweat glands, but although perspiration not infrequently occurs during the fall of temperature under the new antipyretics, this is merely a secondary result here, for when the perspiration is checked by atropine, the fall of temperature proceeds uninterruptedly.

The temperature in healthy warm-blooded animals is kept uniform through a balance being established between the heat formation and its dissipation through the lungs, skin, and other organs. If an excessive formation occurs, as during muscular exertion, this is counterbalanced by an increase in the output from the skin through the dilatation of

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the vessels and by the perspiration. If, on the other hand, more heat is dissipated than usual through exposure to cold, the combustion of the tissues is increased and more heat is formed. The output of heat is thus determined by the degree of dilatation of the cutaneous vessels and the activity of the sweat glands, while the amount of heat formed varies with the voluntary and involuntary contractions of the muscles. In order to preserve a balance between these two factors, there must exist a coördinating mechanism, and this is located in the hypothalamus which contains several centers involved in the control of the body temperature.

Antipyretic Action.—In the normal animal the temperature is kept uniform by a coördinating mechanism, which controls both the output of heat through the skin and its formation by the contractions of the skeletal muscles. In many individuals this coördination is not perfect in health, and in all it may be disorganized by poisons, such as those formed in **fever.** The more perfect the coördination, the smaller is the divergence from the normal temperature necessary to elicit a protective increase in the production or in the dissipation. The efficiency of the mechanism may, therefore, be measured by observing what fall of the body temperature occurs before shivering sets in, what rise produces dilatation of the cutaneous vessels and perspiration. In this way it has been found that during fever the coördination is quite as perfect as in health, but that the protective reactions are induced at a higher temperature. The same measures are taken to preserve a uniform temperature as in health, but the temperature maintained by these means is higher. If a comparison be made with the thermostat of the laboratory, it may be said that in fever the mechanism is "set" for a higher temperature than in normal life, but that the apparatus acts efficiently for each temperature. The higher temperature is maintained by an increased metabolism or heat formation, and also in most cases by a lessened dissipation. The fever temperature itself increases the metabolism, the tissues undergoing more rapid waste under it than in normal conditions. The coördinating mechanism appears to be more susceptible to various influences in fever, and the consequent variations in its activity cause the large undulations of the temperature curve which are characteristic of pyrexia. Among these influences is the temperature itself, for Barbour has shown that the overheated blood tends to change the activity of the center so that the heat loss is augmented.

The antipyretics do not lower the temperature by reducing the heat production, for, though the nitrogen eliminated and the oxygen absorbed fall during their action in fever, this lessened tissue waste is the result, not the cause of the fall of temperature, the metabolism proceeding more slowly when the temperature is reduced.

Calorimetric investigations have shown that the dissipation of heat in fever is much increased by the antipyretics, while in health they seem to have little effect. This augmentation in the output is due to dilatation of the cutaneous vessels, which exposes a large amount of blood to the cold air. The dilatation is great enough to be recorded by the plethysmograph in many cases, while in others flushing of the

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skin may be observed. The increased dissipation of heat is accompanied by a lessened formation which, however, is much less important and which is generally attributed to the metabolism proceeding less actively at the lower temperature. In other words, the antipyretics reduce the temperature by increasing the output of heat, and the cells of the body grow and change less when removed from the hot-house temperature to which they have been exposed previously. It must be added, however, that some observers hold that the fall in heat formation is too great to be explained in this way, and suppose that the antipyretics lessen the combustion through some other action, but not by affecting the tissues directly. And Barbour states that the heat formed may actually increase under antipyretic treatment; this is usually masked by the increased heat loss, but in cases of abnormally low temperature, when the heat loss is not increased by antipyretics, it may actually lead to a rise of temperature under the drug.

It has been stated already that the fevered animal resists any change in its temperature in the same way as the normal, and it might therefore be expected that when the temperature is reduced by antipyretics the organism would at once increase its heat formation. The fact that this does not occur, but that, on the contrary, the metabolism is lessened, indicates that some further change occurs, that the antipyretics not only reduce the temperature by allowing the heat to escape, but also alter the condition of the coördinating mechanism by which the temperature is kept uniform. To return to the comparison with a thermostat, the body temperature is set at a lower point by the antipyretics, while it is set higher by the fever poisons.

The action of the antipyretics on this coördinating center is therefore of interest, and has been examined both in health and disease. In healthy men the temperature does not undergo any marked change under the antipyretics, for though it may fall a few tenths of a degree in some cases, this is of no significance. The sensitiveness of the coordinating center is apparently increased, however, for in some individuals in whom hard muscular work causes a rise of temperature normally, this is absent or less marked after the antipyretics. In the same way the rise of temperature which is occasionally caused by very hot baths is absent or diminished when antipyrine has been administered previously. When the basal ganglia are cut off from their connections with the lower part of the body, neither septic infections not antipyretics have any effect on the temperature, while after section above the basal ganglia, fever is caused, and the antipyretics induce the usual fall of temperature. In experiments in which high fever was produced by lesions in the neighborhood of the ganglia, Gottlieb found that the antipyretics reduced the temperature and increased the output of heat to a marked extent, while the formation was increased to a less degree. Further evidence that the antipyretics act on the regulating mechanism in the brain is afforded by experiments in which they were injected directly into the neighborhood of the centers, when much smaller quantities sufficed to reduce fever temperature than were necessary when they were carried to them by the blood.

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Finally, the condition of the center has been examined by Stern and Richter after the temperature had been reduced by antipyretics. They both found that the protective mechanism was called into play when the temperature was slightly raised, and generally when it was depressed. For example, a fevered dog (temperature 40.9° C.) received an antipyretic, and its temperature was reduced to 37.6°. Attempts were now made to raise the temperature by external heat, but the animal resisted this by increasing the output as soon as the temperature rose to 37.8°. The coördination which maintained the temperature at 40.9° before the drug was administered now attempted to keep it at 37.6°.

The results of these researches may be summed up briefly as follows: The antipyretics reduce the temperature in fever through alterations effected in the heat-regulating nervous mechanism, which result in lowering the point at which the temperature is maintained. As a consequence of this action, a great increase in the dissipation of heat must occur in order to free the body from the warmth which it has

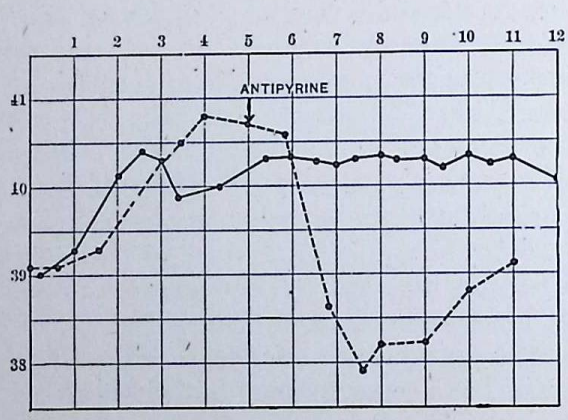

FIG. 70.—Temperature charts of two rabbits under fever toxins. The unbroken line was obtained from an untreated animal, the dotted line from one which received antipyrine at the point indicated by an arrow. The time is given in hours along the horizontal line; the temperature in degrees Centigrade on the vertical. (After Kiliani.)

accumulated, and this increased output is attained by dilatation of the cutaneous vessels. The seat of action of the antipyretics is probably situated in the hypothalamic centers.

Both antipyretics and fever toxins act upon the temperature-regulating mechanism, the one exciting, the other depressing it; the antipyretics may thus be regarded as acting as antagonists to these toxins in the brain in the same way as atropine antagonizes pilocarpine in the heart. The center poisoned by the toxins is apparently more readily acted on than in the normal condition. The toxins are often regarded as stimulating, the antipyretics as depressing the center, but there are equally valid grounds for reversing the rôles and holding that the toxins depress and the antipyretics stimulate it (Barbour).

When the temperature is depressed too rapidly by these remedies, a condition of collapse is often produced, while in other cases the loss of heat caused by the dilatation of the skin vessels seems to be excessive, and shivering and rigor follow in order to increase the production.

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When the temperature has reached the new point fixed by the coördination under the influence of the antipyretics, the heat dissipation rapidly diminishes and may become less than normal, because the new temperature is maintained at a constant point by the same mechanism as the normal.

The antipyretics are rapidly absorbed, and as rapidly **Excreted** by the kidneys, so that they disappear from the body within twenty-four to thirty hours after their administration.

The fate of antipyrine seems to differ in different animals. In the dog it is found to be partially oxidized to oxyantipyrine which is excreted in the urine in combination with glycuronic and sulfuric acids. In others it is said to be excreted in the urine unchanged. Acetanilide undergoes a partial oxidation, the final product differing in different animals, but none of the original body appears in the urine except after very large doses. In man it appears as para-aminophenol and its compounds in combination with sulfuric and glycuronic acids. In the rabbit's urine para-aminophenol alone is found, while in the dog this is accompanied by oxycarbanil ($C_6H_4O.NH.CO$); in each case it forms a double sulfate or glycuronate. The fate of the other antipyretics resembles that of acetanilide, the quinoline derivatives undergoing a partial oxidation resulting in a body analogous to para-aminophenol, while the phenetidine compounds are partially decomposed and appear in the urine as glycuronates of phenetidine. The combinations containing salicylic acid break up in the body, and the acid appears in the urine, while the rest of the molecule undergoes the usual partial oxidation.

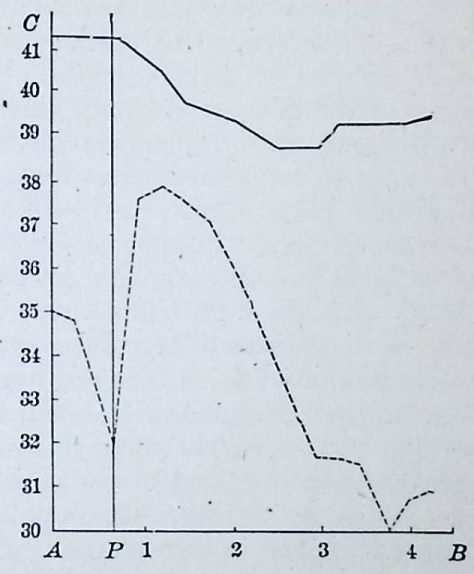

FIG. 71.—Curve of internal temperature (unbroken line) and of the skin temperature (dotted line) in fever treated with antipyrine (Rosenthal). The abscissa *AB* represents the time in hours; the vertical, *AC*, the temperature, Centigrade. At *P*, antipyrine was given, and the skin temperature rose at once (augmented heat output). The internal temperature soon began to fall, and after it had reached a certain point the skin temperature fell again as the vessels contracted.

The presence in the urine of these bodies, or rather of further products of their oxidation, gives it a dark, reddish-brown color, which may be observed when it is passed, or more frequently after it has been exposed to the air for some time.

Therapeutic Uses.—The antipyretics were introduced to **Reduce the Fever Temperature.** The most satisfactory results are obtained from those which act somewhat slowly, but which preserve a low temperature for some time, and the phenetidine compounds are thus preferable to the earlier remedies, which produce a more abrupt fall, after which the temperature soon regains its former height. The best effects are obtained when the antipyretic is given at the commencement of a natural remission, the temperature often falling 2 to 4° F. in the course of the next two to three hours, and only rising slowly afterward. In some fevers

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the antipyretics have much less tendency to lower the temperature than in others. Thus in septicemia larger doses are required than in typhoid and not infrequently no satisfactory reduction of the temperature follows the administration of the maximal quantity. Pneumonia is also said by some writers not to be affected so easily as some other febrile conditions in which the heat-regulating center appears to be in a less stable condition, as is manifested by the occurrence of large spontaneous variations of temperature. The fever of subacute bacterial endocarditis, on the other hand, responds well to the administration of amidopyrine. The reduction of the temperature by the antipyretics lasts only as long as the drug is present in sufficient quantity in the body, and accordingly as soon as sufficient has been excreted, the intoxication of the regulating mechanism begins again, and the temperature soon rises to its former height. The antipyretics do not act on the cause of the disease, but only remove one of the symptoms, but this in itself is not an argument against their use, as is apparently believed by some writers, because as long as the physician is unable to treat the cause directly, he is justified in taking such measures as are possible to remove the symptoms, rather than in adopting an expectant treatment, pure and simple. The extensive use of these remedies shows very clearly that the high temperature is merely a symptom of disease, and not the disease itself, and the question has been much debated whether the reduction of fever is in any way beneficial. No one questions that some antipyretic measures should be taken when the temperature rises so high as to form a danger in itself, but their value in ordinary fever cases is doubtful, and many physicians deprecate their use except in exceptional conditions. The very large doses formerly used undoubtedly induced dangerous symptoms occasionally, but there is little risk of this occurring from the intelligent use of the less violent members of the series. The use of the antipyretics does not retard the formation of the protective substances (antitoxin) to which the recovery from fever is attributed, for in infected animals treated with enormous quantities of antipyrine the serum displays the same agglutinating properties toward the bacilli as that of controls which were not subjected to any medication.

A more serious argument against their use in fever is that the course of the disease is less readily followed, because one of the guiding symptoms—the temperature variations—is no longer dependent solely upon the severity of the intoxication with the fever poisons, and both diagnosis and prognosis are thus rendered more difficult. For example, in typhoid fever a sudden fall of temperature often gives the first indication of such a complication as perforation, but if an antipyretic has been given beforehand, the significance of such a fall in temperature may not be properly appreciated. On the other hand, it is urged in favor of the antipyretic treatment that the patient feels more comfortable and easier when the temperature is reduced, and that this alone may favorably influence the course of the disease. Besides, the high temperature in itself increases the tissue waste and causes larger draughts on the resources of the patient than would be made with the same

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amount of poison in the tissues at a lower temperature; and although the influence of the high temperature on the metabolism was undoubtedly exaggerated at one time, this consideration is by no means devoid of weight.

The antipyretic treatment of fever is of value, then, in cases where the temperature is so high as to endanger life, in cases in which the rise of temperature is the chief cause of distress and no complications are to be apprehended, and, in general, in cases in which the increased comfort of the patient is not counterbalanced by its obscuring the diagnosis and prognosis. On the other hand, there is no reason to suppose that the antipyretics lessen the mortality or shorten the course of most fevers, or that they prevent complications of any kind except excessively high temperature, and the routine treatment of fever with antipyretics is to be deprecated.

The chief rival of the antipyretics in the treatment of fever is the so-called cold-bath treatment, in which the fever patient is placed in a bath of cold water or is sponged frequently with water the temperature of which varies from 70 to 80° F. The fever temperature generally falls to a considerable extent under this treatment, and very often a general improvement in the symptoms occurs. The effect on the temperature is due mainly to the abstraction of heat from the body, and thus far corresponds to that of the antipyretics. In the cold-bath or cold-sponge treatment, however, the loss of heat is not immediately due to the dilatation of the skin vessels, for baths at 70° F. have the effect of constricting the vessels primarily, whatever may be the subsequent effect. The heat output is increased here from the change in the external medium, and not from any alteration in the skin itself. The fall of temperature is generally not so great as under the antipyretics, and the regulation is not directly affected, for the patient shivers and becomes cyanotic long before the normal temperature is reached. The therapeutic virtue of the cold bath was formerly believed to lie exclusively in the abstraction of heat and the fall of temperature, but many advocates of the treatment now hold that this is of less importance than the effects on the circulation, respiration and the brain, which are elicited reflexly by the cold water applied to the skin. The whole nature of the fall in temperature, however, is different from that produced by the antipyretics, and the metabolism, instead of becoming less active as it does under the latter, rather tends to increase under the cold baths, at least as far as the tissue change can be measured by the nitrogen excreted. Each method of treating fever has its advantages, but however the matter may stand in hospital practice, in which trained assistance is available, the antipyretics have a great advantage in many cases in which treatment has to be carried out without any such facilities, for the administration of these drugs may, of course, be entrusted to ordinary persons, whereas the cold bath can be given only by trained attendants. The sponging with cold water is, of course, much simpler. However, in the milder fevers, where no complicated measures, such as the cold bath, are considered necessary, the antipyretics give relief to the patient by removing the feeling of heat and discomfort,

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Although the antipyretics were introduced primarily to lower fever temperature their great importance today arises from the fact that they are used more extensively to relieve certain forms of **Pain.** The analgesic action of these bodies is apparently quite different from that of morphine but the action, while different, is in its way just as specific as is the morphine action. It is of course true that in many instances in which the morphine is successful they fail to alleviate the condition. On the other hand antipyrine and its allies can often be used where morphine is contraindicated, either from the danger of the habit being formed, or from the somnolence it induces. They were first used in neuralgic pain and headache, but have been found equally efficient in other forms of pain and discomfort, and the relief given in fever appears to arise from this analgesic action as much as from the reduction of the temperaturie. In very severe pain and especially in those forms in which it areses from spasmodic contraction of hollow organs, the antipyretics are of little service, while pain arising from affections of the nerves is more amenable to their action. Acetophenetidin and its allies are frquently used for the purpose, antipyrine less often at present; acetanilid should be employed with care. Acetylsalicylic acid has been the most widely used of the group. Caffeine is often prescribed along with the antipyretics in headache and neuralgia. The mixture of 0.2 gram acetanilide, 0.03 gram caffeine and 0.06 gram sodium bicarbonate comprising the **Compound Acetanilid Powder** of the National Formulary. A mixture of 0.12 gram each of acetophenetidin, acetylsalicylic acid and caffeine citrate is also prescribed widely as an analgesic in respiratory infections, influenza, dysmenorrhea and similar conditions.

The antipyretics have been used for their analgesic action in infections generally, and, although they may reduce the temperature, they do not prevent the other symptoms and do not remove the cause of the disease.

The occurrence of agranulocytosis and occasionally collapse and other symptoms has led to a considerable amount of distrust of the antipyretics among many of the medical profession. Unfortunately, this distrust is not entertained by a large class of the laity, and numerous cases of poisoning arise from the impression that the antipyretics are not dangerous drugs. For the most part, poisoning seems to be due to a peculiar sensitiveness or idiosyncrasy, which cannot be foreseen, but in cases of great exhaustion and asthenia, especially when accompanied with anemia, these drugs have to be used with care.

Preparations

U. S. P.

Antipyrina, antipyrine, phenazone, a white crystalline powder. Dose, 0.3 gram (5 gr.).

Acetophenetidinum, acetophenetidin, phenacetin, a white crystalline powder. Dose, 0.3 gram (5 gr.).

Tabellæ Acetophenetidini, acetophenetidin tablets, phenacetin tablets. Dose, 0.3 gram (5 gr.).

Acetanilidum, acetanilid, antifebrin, a white crystalline powder. Dose, 0.2 gram (3 gr.).

Aminopyrina, aminopyrine, amidopyrine, a white crystalline powder. Dose, 0.3 gram (5 gr.).

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B. P.

PHENAZONUM, phenazone, antipyrine. Dose, 0.3 to 0.6 gram (5 to 10 gr.).

TABELLÆ PHENAZONI. Dose, 0.3 to 0.6 gram.

PHENACETINUM, phenacetin, acetophenetidin. Dose, 0.3 to 0.6 gram (5 to 10 gr.).

TABELLÆ PHENACETINI. Dose, 0.3 to 0.6 gram.

AMIDOPYRINA. Dose, 0.3 to 0.6 gram (5 to 10 gr.).

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Q. SALICYLATES

Salicylic acid was introduced into medical use as a substitute for carbolic acid, but its chief interest now lies in the use of its sodium salt in acute rheumatic fever. Some of the esters have also been employed; *methyl salicylate,* which is found in the volatile oil obtained from the *wintergreen* (*Gaultheria procumbens*) and from *birch bark* (*Betula lenta*) and which is also formed synthetically; *phenylsalicylate* or *salol,* formed synthetically; the numerous other salicylic esters which have been introduced by enterprising manufacturers have not attained a wide use. The compound which has been most widely employed is *acetylsalicylic acid,* or *aspirin. Salicin,* $C_{13}H_{18}O_7$, is a glucoside found in the poplars and willows, which forms salicylate in the body and has had a limited use.

Local Action.—Salicylic acid has some value as an antiseptic, largely from its acidity, and the neutral salts are almost devoid of this property; thus protein solutions do not putrefy and the alcoholic and acetic acid fermentations are retarded by comparatively small quantities of salicylic

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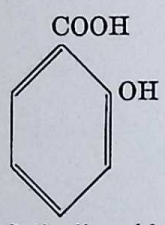
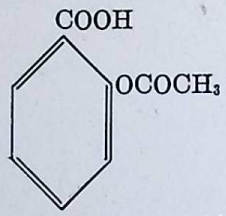
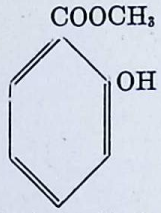
acid, while the salicylates are almost inert. The salicylic preparations are generally less efficient than phenol in the presence of proteins, probably because the latter is more volatile and forms less stable combinations and therefore penetrates more readily. Salicylic acid, on the other hand, does not evaporate and therefore preserves objects which are exposed to the air for a longer time than does carbolic acid, which is soon dissipated. The movements of plant protoplasm, protozoa and leucocytes are prevented by salicylic acid, which also retards the digestion of proteins by the gastric and pancreatic juices, and the decomposition of glucosides by ferments, but this is probably due to its acidity and not to the salicylate ion.



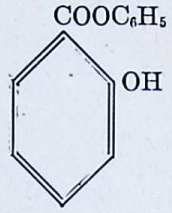
Salicylic acid



Acetylsalicylic acid (Aspirin)



Methyl salicylate (Oil of wintergreen)



Phenylsalicylate (Salol)

Irritant Action.—When salicylic acid is applied for some time as a powder to wounds, mucous membranes, or even the skin, it may induce corrosion and necrosis. It sometimes causes soreness and irritation of the mouth and throat when swallowed in powder, and congestion and even erosion of the mucous membrane of the stomach have been observed; even dilute solutions often cause pain and discomfort in the stomach. Sodium salicylate is only very slightly irritant, but when it is swallowed, some of the acid is liberated by the hydrochloric acid of the stomach and may be deposited on the mucous membrane and give rise to acute dyspepsia.

Symptoms.—Salicylic acid and its salts are rapidly absorbed from the intestine and as a general rule produce no symptoms, unless when given in large doses. Some individuals, however, are peculiarly sensitive to the action of the salicylates, and in these comparatively small doses are followed by symptoms which are generally of only slight importance, but which are sometimes sufficiently grave to cause anxiety, and in very rare cases have been followed by death.

The ordinary symptoms are nausea, vomiting, and sometimes diarrhea; a feeling of heaviness and fullness in the head, with hissing or roaring sounds in the ears exactly resembling those produced by quinine. These may be followed by some confusion and dulness and by indistinct sight and hearing. Very often the patient complains of excessive perspiration and a sense of warmth all over the body. Dyspnea, marked by exceedingly deep and labored respiration, has been noted in more serious cases of poisoning, and a condition of collapse with slow, weak pulse, subnormal temperature, and partial or complete unconsciousness may follow. In others, delirium and hallucinations of sight and hearing have occurred, these being more frequently seen in chronic alcoholic patients and in cases of diabetes than under other conditions. Albumin,

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casts and even hemoglobin and blood in the urine are often noted as sequelæ. Various forms of skin eruptions have been described as occurring under the use of salicylic acid, sometimes after a single dose, but more frequently after prolonged treatment. They resemble those seen under the antipyretics, but seem to be less frequently elicited by salicylic acid. Hemorrhages from the nose, mouth, stomach, intestine and uterus have also followed the use of this drug, and the last may explain the occasional occurrence of miscarriages under it; it has no influence on the uterine movements in the concentrations found in the blood in man, though stronger solutions increase the contractions in animals.

The hemorrhagic tendency which follows the administration of large doses of salicylate is in part due to the **hypothrombinemia** induced by the drug. This decrease in the prothrombin level of the blood gives a prolonged bleeding time which, with vascular dilatation and injury may be responsible for the observed tendency to hemorrhage.

Deaths have been reported in patients receiving large amounts of salicylates for rheumatic fever in which at autopsy hemorrhage in the brain has been observed (Ashworth and McKemie). The prothrombin deficiency can be prevented by the administration of large doses of vitamin K.

The **fatal dose** of salicylate is variable. In 752 cases of attempted suicide with acetylsalicylic acid reported by Balaz, four were fatal in which 20 to 40 grams of the drug were ingested. Recovery, however, has followed the taking of 80 grams of the drug (Hopkins). On the other hand, in the 30 cases of poisoning reported in the literature (Bowen, *et al.*) the fatality rate was about 50 per cent.

In animals, salicylates injected intravenously cause some acceleration of the pulse and respiration, followed by slowness and weakness of the heart, and often by marked dyspnea. Depression of the central nervous system is shown by slowness, weakness, and incoördination of the spontaneous movements, and eventually by stupor and arrest of the respiration, which is generally preceded by convulsions. Photophobia and clonic spasms have been observed in some dogs. Hyperemia of the kidney, liver, brain and tympanum are sometimes found at the autopsy on dogs poisoned with salicylates and when the drug has been given in powder, congestion, irritation, and necrosis of the gastric mucous membrane. This irritation of the stomach often causes vomiting in dogs, and the poison being thus eliminated, no further symptoms appear. Vomiting occurs in cats when salicylate is injected hypodermically, which indicates some action on the medullary centers; increased reflexes, tremors and restlessness are also described in these animals in which a more distinct stimulation of the central nervous system seems to be elicited than in man.

In the frog, salicylic acid produces quickened respiration and increased reflexes, followed by depression of the spontaneous movements, tremor, and clonic contractions. The heart is slow, dilated, and weak.

The symptoms elicited by salicylic acid and its salts although very indefinite occur not infrequently in man. The salicylates exert a profound effect on the enzyme systems of the body (Lutwak-Mann) and many of the observed toxic effects are probably to be attributed to this action.

The **Disorders of Hearing** have been ascribed to congestion of the

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tympanum, but may perhaps indicate some changes in the nerve cells of the ear analogous to those observed under quinine. As a general rule they pass off in the course of a few hours or days, but they sometimes leave a more or less permanent impairment of the sense of hearing. The **Dimness of Sight**, sometimes amounting to complete blindness, is due to vascular or retinal changes in the eye (see Quinine), and some disturbance of the circulation of the brain and head may be the cause of the dulness and fullness of the head complained of, and of the not infrequent epistaxis. Maragliano showed by plethysmographic measurements that the **Vessels of the Skin** are dilated by salicylates in the same way as by the antipyretics.

With small therapeutic doses of the salicylates the **Circulation** is little altered unless in a susceptible individual, when the heart may be somewhat accelerated. Full therapeutic doses may cause some depression of the circulation, but usually this is not important. The general **Blood-pressure** may be found to be increased by small quantities of the salicylates from stimulation of the vasoconstrictor center, while after very large injections into the blood-vessels, the pressure is lowered, partly perhaps from depression of the center, but mainly from the cardiac action of the drug.

Small quantities may accelerate the **Heart** in animals in the same way as small doses of the other aromatic bodies, apparently from direct action on the cardiac muscle. Very large doses produce a slow, weak, and dilated heart, and a corresponding fall in the blood-pressure. Friderichsen found that 0.12 per cent of salicylate in the blood causes no symptoms from the heart, but any higher content is injurious.

The acceleration and deepening of the **Respiration** and the dyspnea which have been noted in man, seem to be due to central action, either from a direct stimulation of the center by the salicylate or from an indirect effect due to some products resulting from the activity of the drug. There is sometimes a feeling of shortness of breath or dyspnea. In animals, too, the respiration is first accelerated to some extent, and then slowed, apparently from the respiratory center being first excited, then depressed, and eventually paralyzed, by very large quantities of the drug. In the early stages of respiratory acceleration there is a marked increase in pulmonary ventilation but this increase may not keep pace with the increase in respiratory rate. In certain cases the tidal air is below normal. Death seems to be due to respiratory paralysis, the heart continuing to beat for some time afterward. Although the alkali reserve of the blood is reduced even with small doses of sodium salicylate, this apparently is not the cause of the observed hyperpnea, nor is it always associated with ketosis which occurs only sporadically (Fashena and Walker).

The effects of salicylates on the **Central Nervous System** seem to be comparatively slight, except in cases in which a special idiosyncrasy exists. No such convulsive action as occurs under others of the aromatic series has been observed under it, and in animals there seems no marked depression save in the medulla oblongata. The convulsions which are observed before death are probably not due to the direct

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action of the drug, but to the asphyxia. In the medulla oblongata the respiratory and vasoconstrictor centers, and probably the vasodilator, seem to be first stimulated and then depressed.

The **Perspiration** which so often follows the administration of salicylic preparations may be due in part to the dilatation of the skin vessels, but is probably to be ascribed rather to increased activity of the sweat centers. Some of the **Skin Rashes** may also be caused by the dilatation of the cutaneous vessels which perhaps induces the appearance of an eruption in individuals who are predisposed to them. Erythema, desquamation and acne may occur.

Salicylic acid and its salts may increase to some extent the **Secretion of the Urine**, probably through a direct action on the renal epithelium. Polyuria followed by oliguria and anuria is an early manifestation of poisoning. Very frequently the effect of the administration of full therapeutic doses of the salicylates is to lessen the quantity of urine. This action is probably due partially to the diaphoresis and partly to a direct action on the kidney. The latter action is shown not only by albuminuria but also by an increase in the urea in the blood and by a diminished excretion of phenolsulphonphthalein. Nephritis has been observed in some cases, with not only albumin but also blood in the urine. The administration of bicarbonate of soda with the salicylate does not appear to lessen the tendency to renal irritation in any way.

Experimental studies have demonstrated the nephrotoxic action of salicylates, especially for the kidneys of dogs. It is apparently more toxic for the kidneys of these animals than are the cinchophen compounds, although this relationship does not hold for all species, the rat apparently forming an exception (Barbour and Fisk).

The salicylic preparations produce a slightly augmented flow of **Bile**, apparently from some specific action on the liver cells. The bile is generally more dilute than normal, the fluid increasing more than the solids, though the total solids excreted are augmented.

Salicylate has been said to lower the normal **Temperature**, but this seems to be erroneous, except when very large quantities produce a condition akin to collapse. In fever patients, however, it often causes a marked fall of temperature, and it was formerly used as an antipyretic for this reason. The action is probably explained by the dilatation of the cutaneous vessels, and the increase in the output of heat. (See Antipyretics.) Dilatation of the skin vessels also occurs in normal persons after salicylates, but this is counterbalanced in them by increased heat formation. The fall in temperature after salicylic acid is generally less in extent and of shorter duration than that following the members of the antipyrine series.

An interesting fact, pointed out by Barbour, is that persons with unstable temperature centers, such as those persons who are only temporarily afebrile or who are convalescent, react to acetylsalicylic acid in the same manner as do febrile patients; that is, their heat elimination is greatly increased, perhaps 40 per cent, while in normal persons the elimination of heat may not be altered.

In its passage through the tissues, salicylic acid modifies the **Metab-**

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olism, as is shown by an increase of 10 to 12 per cent in the nitrogen and sulfur of the urine. This indicates a considerably augmented decomposition of the proteins of the body, accompanied by an increased metabolic rate of 20 to 25 per cent. A still more notable augmentation of the uric acid excretion has been observed, different authors estimating it at 30 to 45 and even 100 per cent. This occurs also in animals and persons on a purine-free diet; the uric acid escapes through the kidney more easily, and the percentage in the blood falls as that of the urine rises. (See Cinchophen, p. 669.)

Salicylate circulates in the blood as the sodium salt; most of it is carried in the plasma, but some passes into the corpuscles; it does not accumulate in the joints more than elsewhere, as was once believed. It is found in practically all secretions and organs of the body; the brain is said to contain less than most of the other organs, averaging perhaps a third as much as is found in the muscles, blood or spleen. About three-fourths of that ingested is **Excreted** by the kidneys, for the most part unchanged. Part of the drug is oxidized further to dioxybenzoic acid and to hydroquinone and part is excreted in combination with sulfuric and glycuronic acid. It appears in the urine within an hour of its administration by the mouth and is all eliminated in forty-eight hours. It has been found also in the milk, perspiration and bile, but does not appear to be excreted into the stomach, nor is any found in the feces. About 20 per cent or more is completely destroyed in the tissues, and this fraction is higher in rheumatic fever than in normal persons; the actual concentration in the blood and urine may thus be lower in rheumatic fever.

Methyl Salicylate (oil of wintergreen) has a hot, burning taste, and like other volatile oils produces a feeling of warmth in the stomach. In many cases it is well borne, but some patients complain of pain in the stomach, loss of appetite, and even nausea and vomiting. Much of it is decomposed to salicylate in the intestine and this is rapidly absorbed and produces the characteristic symptoms in large doses. Much less salicylate is excreted in the urine than after the corresponding sodium salt, and some of the oil reappears unchanged.

The methyloxymethyl ester of salicylic acid resembles methyl salicylate but is more irritant. It is absorbed from the skin but is used mainly for its local action as a counterirritant in rheumatic conditions. It is a clear yellowish oily fluid which is diluted with from 1 to 4 parts of olive or cottonseed oil before being applied to the skin. Care must be taken not to use friction in applying it and not to repeat the application too often in the same place.

Salicin, a glucoside found in many species of willow and poplar, is decomposed into salicyl alcohol, which is oxidized to salicylates in the body. It is probable that the decomposition, like that of the ordinary esters, takes place chiefly in the intestine, for when it is injected intravenously it is excreted unchanged. It is very bitter, but does not irritate the mucous membranes, and is not so certain in its action as salicylate. When administered by the mouth it is excreted in the urine partly as salicin, partly as saligenin or salicyl alcohol, and partly as salicylic and salicyluric acids. It is little used in therapeutics today.

Acetylsalicylic Acid, or **Aspirin**, passes through the stomach unchanged and is free from the gastric effects of salicylic acid and the salicylates. It is partially decomposed into salicylic acid in the bowel, but some of it is absorbed in its original form. The salicylate formed from it exercises

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its usual action in the tissues, but there is a further action resembling that of the antipyretics in headache and neuralgia, and this is attributed to the action of the acetylsalicylate which has escaped decomposition and has been absorbed.

Symptoms of **idiosyncrasy** to acetylsalicylic acid are more common than to the other salicyl compounds. The principal manifestations of this hypersensitivity are urticaria, asthmatic attacks, angioneurotic edema, etc. These tend to occur in allergic individuals although many of the latter may take the drug with impunity (Prickman and Buchstein). Congestion of the nose with localized edemas are most commonly encountered. These latter edemas may involve the eyelids, pharynx, lips, or the extremities.

Salysal is the salicylic ester of salicylic acid. It resembles the other salicylates quite closely in its general effects, but being insoluble in water it is practically tasteless and is relatively free from local irritating effects.

The isomers of salicylic acid, **meta-oxybenzoic** and **para-oxybenzoic acids** which differ from salicylic acid which is the ortho derivative, are devoid of therapeutic activity. This difference in activity between the isomers of the benzene series is very frequently met, and the relative toxicity differs in the different compounds; thus the ortho-compound is most active in the oxybenzoic acids (salicylic acid), while among the cresols the metacresol is said to be the most poisonous, and parachlorphenol is more antiseptic than either of its isomers.

The three isomeric **cresotinic acids** ($C_6H_3.CH_3.OH.COOH$) that correspond to salicylic acid in the position of their hydroxyl and carboxyl groups, resemble it in action and are effective in acute rheumatism; they are approximately equal to salicylic acid in toxicity, but ortho-cresotinic acid has a more depressant action on the heart, and as they offer no advantages over salicylates, they have only been used experimentally in therapeutics.

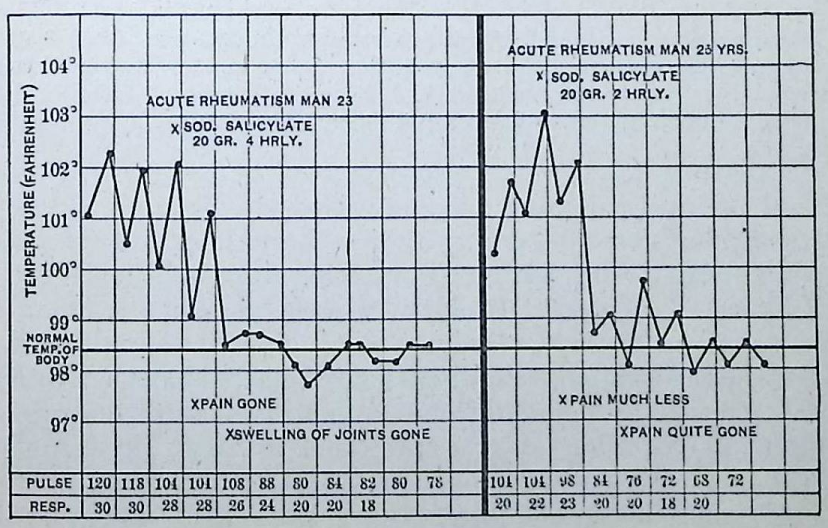

FIG. 72.—Clinical charts of cases of acute rheumatic fever treated with salicylate of sodium Case 1, 1.3 grams every four hours; Case 2, 1.3 grams every two hours. (Stockman.)

Therapeutic Uses.—The chief sphere of usefulness of salicylate at the present time is in the treatment of **acute rheumatic fever**, in which it seems to have a specific action similar to that of colchicum in gout. Some other members of the aromatic series are useful in this condition,

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but none is superior to the salicylic preparations in efficacy. Under this treatment the pain, swelling, and redness in the joints rapidly lessen, the temperature often falls, and the disease makes less demands on the strength and courage of the patient. It is a question whether it acts on the unknown cause of the disease, and some hold that it is a purely symptomatic treatment and that salicylate may be replaced by a mixture of other antipyretic and analgesic remedies, although experience seems to indicate that none of the members of the antipyrine group is as efficient in relieving the pain and discomfort in this condition as are the salicylates. It is still debated whether the salicylate treatment reduces the liability to involvement of the heart, which is a common complication of acute rheumatic fever. It is generally believed now that the incidence, extent, and prognosis of cardiac damage are affected by the use of the salicylates, and most clinicians believe that the cardiac affections are less often met with and are less severe under salicylate treatment.

Although the sedimentation rate is markedly lowered by the administration of salicylates in the initial attack it is little affected in recurrent attacks of polycyclic rheumatic fever.

Dosage.—Large doses of sodium salicylate or acetylsalicylic acid are required in the treatment of acute rheumatic fever. A convenient rule for sodium salicylate dosage is to give a grain per day per pound of body weight (0.14 gram per kilo). This is divided into equal doses given at three- to four-hour intervals.

Coburn has advocated the use of massive doses of sodium salicylate (10 to 20 gr. daily) to maintain a blood level above 35 mg. (of salicylic acid) per 100 cc. With this concentration he claims to obtain more rapid subsidence of the rheumatic inflammation. Although blood levels below 20 mg. per 100 cc. suffice to relieve symptoms, Coburn believes that the higher concentration is required to suppress the "rheumatic reaction." A dose of 10 grams (150 gr.) daily in an adult will in most instances maintain a blood level of 30 to 50 mg. per 100 cc. (Butt, *et al.*).

After the acute symptoms have subsided the drug should be continued in smaller doses 0.6 gram (10 gr.), three times daily, for several weeks or months. This continued administration is believed to lessen the likelihood of relapses. Children in general seem to tolerate the salicylates well and to take relatively larger doses than could ordinarily be given when calculated according to their age. The effective dose of acetylsalicylic acid in rheumatic fever is about two-thirds that of sodium salicylate, but the latter drug is preferred by many in this disease. Salicylic acid should not be given, as it is more irritant to the stomach.

Sodium bicarbonate is frequently recommended along with the salicylate on the ground that it lessens the gastric irritation by preventing the formation of the irritant salicylic acid. However, it has been claimed that the concurrent administration of bicarbonate decreases materially the blood levels obtained from a given dosage of salicylate (Smull, *et al.*), but this has not been confirmed by more recent work.

In other acute constitutional diseases accompanied by fever, salicylate has no such specific action as in acute rheumatic fever; even when the

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joints are involved, as in gonorrheal arthritis, salicylate is of little or no service, so that some special relation appears to exist between the salicylate and the cause of rheumatic fever. However, salicylate does reduce the fever and exerts an analgesic action in conditions other than rheumatic fever. The response to the drug when used as a therapeutic test in patients suspected of having rheumatic fever is thus not conclusive.

Salicylate in some cases promotes the absorption of effusions into the serous membranes, such as the pleura, and also subretinal effusion. It is unknown how this is effected.

Salicylic acid is occasionally applied locally in excessive sweating (2 to 4 per cent in talc) and has also been used in various skin affections in which it is desirable to soften or partially dissolve the epidermis; because of this keratolytic action, it is the chief constituent of many "corn-salves." For this purpose it is best used as a 20 per cent solution in collodion.

Salicylic acid has also been used very largely as a preservative in wine, beer and foods. No evil effects have been shown definitely to follow the prolonged use of substances thus treated, but they may tend to disturb the digestion, and several governments have found it advisable to prohibit its use for this purpose.

Acetylsalicylic acid is used chiefly to relieve headache and neuralgia in the same way as the antipyretic group, and for this purpose may be given in doses of 0.3 to 0.6 gram (5 to 10 gr.) in tablets.

Salicylic preparations have to be used with care where any symptoms of renal irritation are present and large doses should be used with care in cases of pregnancy, as they may lead to miscarriage. In cases of poisoning, the treatment is determined entirely by the symptoms, and no antidote is known.

Methyl salicylate, or oil of wintergreen, is often applied locally in muscular and articular rheumatism. Absorption certainly occurs through the skin, as is proved by the appearance of salicylates in the urine. Several other synthetic compounds have been suggested in place of wintergreen oil in external treatment, but they have no advantage over the older drug.

Preparations

U. S. P.

Sodii Salicylas, a white powder, soluble in water. Dose, 0.3 gram.

Tabellæ Sodii Salicylatis, sodium salicylate tablets. Dose, 0.6 gram.

Acidum Salicylicum, salicylic acid, white crystals slightly soluble in water.

Phenylis Salicylas, phenyl salicylate, salol, a white crystalline powder. Dose, 0.3 gram.

Methylis Salicylas, methyl salicylate, oil of wintergreen, a clear oil.

Acidum Acetylsalicylicum, acetylsalicylic acid, aspirin. Dose, 0.3 gram.

Tabellæ Acidi Acetylsalicylici, acetylsalicylic acid tablets, aspirin tablets. Dose, 0.3 gram (5 gr.).

B. P.

Sodii Salicylas. Dose, 0.6 to 2 grams.

Tabellæ Sodii Salicylatis. Dose, 0.6 to 2 grams.

Acidum Salicylicum. Dose, 0.3 to 0.6 gram.

Acidum Acetylsalicylicum, aspirin. Dose, 0.3 to 1 gram.

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TABELLÆ ACIDI ACETYLSALICYLICI, tablets of acetylsalicylic acid, tablets of aspirin. Dose, 0.3 to 1 gram (5 to 15 gr.).

METHYLIS SALICYLAS. Dose, 0.3 to 1 mil.

SALICINUM. Dose, 0.3 to 1 gram.

UNGUENTUM ACIDI SALICYLICI, 2 per cent salicylic acid in ointment.

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I. Benzoic Acid and Benzoates

Benzoic acid and its salts resemble the salicylic preparations closely in their action in most points, the acid being antiseptic and irritant, while the salts are less active in this respect. Benzoates have less action on the central nervous system, and the disorders of hearing which are characteristic of the salicylates, have not been observed. Nausea and vomiting occur from very large quantities in man, and it is believed that the expectoration is increased by the use of small doses of benzoates in bronchial catarrh.

Benzoic acid (C_6H_5COOH) combines with glycine in the kidney and in other organs to form hippuric acid ($C_6H_5CO—NHCH_2COOH$), which is excreted in the urine; some of the benzoic acid escapes in the urine unchanged, the proportion of hippuric acid formed apparently varying with the dose administered and other conditions; and some appears to be excreted in combination with glycuronic acid when very large doses are administered. The amount which is transformed to hippuric acid does not increase significantly when glycine is administered along with benzoic acid, yet the glycine seems to lessen the tendency to convulsions in animals. In birds benzoic acid is excreted by the kidneys as ornithuric acid

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($C_{19}H_{20}N_2O_4$), from which benzoic acid can be split off, leaving ornithin. Benzoic acid often increases the nitrogen eliminated in the urine, so that in these cases it augments the decomposition of the proteins like salicylic acid; in other investigations no material change has been observed, probably because the benzoic acid was changed to hippuric acid too rapidly to admit of its action on the metabolism being developed. It differs from salicylic acid in reducing the uric acid excretion. Some diuresis occurs after benzoic acid, and the acidity of the urine increases in the same way as after other acids which do not undergo combustion in the tissues.

Benzoic acid has sometimes been employed as an antiseptic, and sodium benzoate has been credited with some virtues as an intestinal and genito-urinary disinfectant. The treatment of gout and other diseases with benzoates on the theory that they lessened the uric acid excretion is obsolete. Ammonium benzoate has been given to increase the acidity of the urine, but is not so useful as the acid sodium phosphate. Benzoic acid is still an ingredient in many expectorant mixtures, generally in the form of benzoin or balsam of Tolu.

Sodium benzoate is used in the **hippuric acid test** for hepatic function. In this test 6 grams are administered, orally, or 1.77 grams, intravenously, and the amount of hippuric acid eliminated in the urine is determined. A diminished output indicates hepatic insufficiency. **Ortho-iodobenzoic acid** in the form of its salts was introduced as a remedy against infectious arthritis. However, because of its violent effects and its doubtful value in arthritis, it is now rarely used for this purpose.

Cinnamic acid (C_6H_5—CH=CH—COOH) seems to resemble benzoic acid in its pharmacological characters, but has not been so carefully examined. It increases the leucocytes of the blood and the uric acid of the urine to a marked degree.

PREPARATIONS

U. S. P., B. P.

ACIDUM BENZOICUM, benzoic acid, white crystals, practically insoluble in water. Dose, B. P., 0.3 to 1 gram.

TINCTURA OPII CAMPHORATA, camphorated tincture of opium, paregoric, contains benzoic acid, camphor, oil of anise, tincture of opium in diluted alcohol and glycerin. Dose, U. S. P., 4 cc.; B. P., 2 to 4 mil.

SODII BENZOAS, sodium benzoate, a white granular or crystalline powder. Dose, B. P., 0.3 to 2 grams.

BENZYLIS BENZOAS (B. P.), benzyl benzoate ($C_6H_5{:}CO_2{:}CH_2{:}C_6H_5$). Dose 0.3 to 0.5 mil.

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R. QUININE AND OTHER ANTIMALARIAL DRUGS

I. QUININE

The barks of various species of *Cinchona* and *Remijia*, trees native to the high altitudes of the Andes, contain numerous alkaloids which resemble each other in their chemical and pharmacological properties. The best known of these are *quinine, quinidine, cinchonine* and *cinchonidine;* the others, amounting to some twenty in number, resemble these in their effects on the organism, but very little has been done to determine this, and little is known regarding their relative activity.

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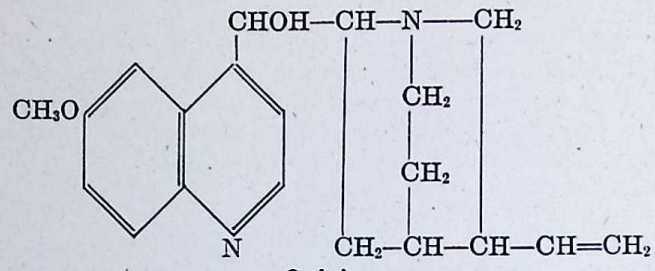
Chemistry.—The parent alkaloid of the series is cinchonine ($C_{19}H_{22}N_2O$), which is isomeric with cinchonidine. Cinchonine consists of a quinoline nucleus linked through a secondary alcoholic group to a quinuclidine ring system to which is attached a vinyl ($CH=CH_2$) group. Quinine ($C_{20}H_{24}N_2O_2$) and its isomer, quinidine, are the 6-methoxy derivatives of cinchonine with the structure shown in the accompanying formula.



Quinine

Besides these alkaloids cinchona bark contains several acids, including tannins, and some neutral substances.

The cinchonas are cultivated in India and Java. The bark of the cultivated trees may contain as much as 10 per cent of quinine and one famous graft contained 18.5 per cent of this alkaloid. It seems questionable whether the virtues of the bark were known by the native Indians before the invasion of the Spanish, and its introduction into medicine dates from about 1630 to 1640; its name bears testimony to its efficacy in the legendary case of the Countess of Cinchon in 1638.

Action.—Quinine differs from most of the other important alkaloids in acting, not on some specialized form of living matter, but on the general nutrition of almost all forms of protoplasm. Other alkaloids, such as strychnine, are also possessed of similar effects as regards nutrition, but their strong affinity for, and intense action on, some special tissue prevent their effects on the fundamental properties of living matter from being elicited in the higher animals. Quinine is therefore often termed a protoplasmic poison because its action extends with but little variation throughout most forms of living matter. The effects of quinine on protoplasm generally consist in transitory augmentation of its activity, followed by depression and death.

The action of quinine on **Undifferentiated Protoplasm**, such as is found in the unicellular organisms and in the ovum, is therefore of greater interest than that of most alkaloids. Binz found that while very minute quantities sometimes increase the movements of the ameba and infusoria at first, large amounts paralyze them immediately, and the protoplasm assumes a darker granular appearance. The rhythmic movements of ciliated organisms are rendered slow and finally arrested by very dilute solutions, and the microbes of putrefaction are also acted upon by quinine, although they are more resistant than the protozoa; still, quinine solutions, 1:2000, delay the growth of bacteria. The alcoholic, lactic and butyric fermentations are similarly retarded, but it is apparently devoid of action on some of the lower forms, for molds (Penicillium) grow freely in solutions of the salts,

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perhaps because the quinine fails to penetrate through the cell membrane. Another example of its action on the vegetable cell is that discovered by Darwin in some insectivorous plants (Drosera), in which the movements seem to be first excited and later paralyzed by the quinine salts.

The influence of quinine on the reproductive cells of animals has been carefully studied by O. and R. Hertwig, who found that both the spermatozoön and the ovum of the sea-urchin are injured by the addition of quinine to the sea-water, the movements of the former being paralyzed, and the stages preceding impregnation in the latter progressing more slowly, or actually retroceding. When quinine is applied after the male nucleus has entered the ovum, the complete conjugation is delayed and the whole process is rendered abnormal by the admission of several spermatozoa. Quinine applied still later prevents or delays the division of the ovum through its effects both on the nucleus and on the general protoplasm of the cell.

The individual cells of more complex organisms are affected in the same way as these more simple ones. This was first demonstrated in the leucocytes by Binz, who showed that when quinine is added to a drop of blood under the microscope, the ameboid movements of the leucocytes are arrested, and they assume a spherical form, become darker in color and granular, and soon break up into débris. In the blood-vessels similar changes occur when quinine is applied locally, as to the frog's mesentery; the leucocytes again become darkly granular, and ceasing their creeping movements, are carried along by the current much more rapidly than usual. They are no longer observed to push their way through the vessel walls, and if they have already penetrated into the tissues their movements are arrested. If irritation be applied to the part, no such accumulation of leucocytes occurs in the tissues as in the unpoisoned animal, and if an irritant has been applied first and the leucocytes have poured out of the vessels before the quinine is applied, the process is arrested at once on its application. This poisonous effect on the leucocytes has received much attention, but only occurs when the alkaloid is present in a concentration of 1:3,000, which is higher than can obtain in the blood of a living animal. Lower concentrations affect some other functions of the leucocytes, whose phagocytic powers are lessened by concentrations of 1:24,000; the bactericidal action of the plasma is also reduced by this concentration. There is no reason to suppose that this action on the white blood cells occurs when quinine is administered in therapeutic doses, which would not give rise to this concentration. All of these effects are greatly influenced by the reaction of the medium, since any increase in its alkalinity increases the toxicity; this may probably be ascribed to the alkaloid penetrating more easily into cells than its salts.

Some enzymes seem to be rendered inactive by quinine; for example, the blood no longer forms the blue oxidation product of guaiac in the presence of quinine in a concentration of 1 per cent. A number of other ferments act more vigorously in very dilute solutions of quinine, while they are retarded by larger quantities; for example, the autolytic fer-

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ment of the liver, pepsin, and rennet. And some appear to be much less susceptible to its action than others, for they are augmented in activity by quantities that retard or destroy those more readily affected.

The action on striated **Muscle** is similar to that on the lower organisms. There is sometimes a transient increase in its power but very soon the muscle contraction is weaker and fatigue follows more quickly than normally. Injections of large amounts of quinine salts into muscle kill the fibers and lead to sloughing. In myasthenia gravis the administration of quinine accentuates the weakness of the muscles characteristic of this disorder.

The **Nerve Trunks** are remarkably tolerant to solutions of quinine, which do not lessen their irritability when applied locally in sufficient quantity to cause marked abnormalities in the muscular contraction. In the frog, the terminations of the motor nerves in striated muscle are paralyzed by large doses, but not in mammals.

Unstriated Muscle in the mammals tends to contract under quinine, this action being especially marked in the **Uterus**, which is thrown into strong rhythmical contraction when it is suspended in Ringer's solution containing quinine. Contractions are also initiated in the resting uterus when quinine is carried to it by the blood in the intact animal and this has led to its use in obstetrics to arouse the relaxed organ. Similarly the excised intestine suspended in Ringer's solution is aroused to increased movement by quinine, but there is no evidence that this occurs when quinine is carried to it by the blood. The spleen contracts, however, in the intact animal and in man, apparently from its acting on the muscle fibers, and quinine perfused through the arteries of an excised organ often narrows their caliber from contraction of the muscle of the walls; this contraction is often followed by relaxation. In each of these cases the action seems to be exerted directly on the muscle, which is first contracted and then relaxed if the dose is large.

The **Heart** is sometimes accelerated in mammals, but is generally slowed and weakened when quinine is injected intravenously; this is due to direct action on the heart muscle, but large amounts may depress the vagus terminations. The heart continues to beat after the respiration has ceased in fatal poisoning. The weakness of the heart leads to a fall in blood-pressure, but the main cause of the fall is dilatation of the peripheral vessels due in part to an action upon the vasomotor endings and in part to a direct action on the muscle fibers themselves. Both quinine and quinidine antagonize the pressor effects of epinephrine as the latter drug fails to cause an increase in blood-pressure following the intravenous administration of the two cinchona alkaloids. The cardiac effects are not observed except in a very slight degree when quinine is absorbed from the stomach even in large therapeutic doses. In the frog also the heart is slowed and weakened from depression of the muscle.

The **Central Nervous System** is found to undergo a slight and transient excitation when large doses are injected in mammals, but the chief effects are of the nature of depression. Thus in the frog a short stage of slightly exaggerated reflex movement is followed by the loss of spontaneous movements, the arrest of the respiration, and paralysis of the

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spinal cord and ends of the motor nerves. In mammals, the spinal cord is stimulated by small quantities and then depressed. The respiration is sometimes quickened at first and later becomes weak and slow and its cessation is the cause of death. General depression and muscular weakness are usually the only cerebral effects observed in mammals and the tremor and convulsions which sometimes occur are perhaps due to the failure of the respiration.

The **Secretions** are not affected by quinine unless very large quantities are injected when they are arrested.

In **Man**, quinine taken by the mouth has the same action on appetite as the simple bitters. Ordinary therapeutic doses often produce no very obvious symptoms, the most frequently observed effect consisting in derangement of the **Sense of Hearing**, less frequently of that of **Sight.** Ringing or roaring sounds in the ears, accompanied by slight deafness, are produced by moderate quantities, and large doses are not infrequently followed by complete loss of hearing for a time. Contraction of the field of vision is observed less often, but in some cases total blindness has been produced and has lasted for several days or even weeks. Color-vision is especially liable to be rendered imperfect or temporarily paralyzed by quinine; these disorders of sight are accompanied by a very marked contraction and even obliteration of the retinal vessels and sometimes by degenerative changes in the retinal nerve cells and even by atrophy of the optic nerve. It is still undecided whether the vascular change or the nervous degeneration is the primary lesion, but the majority of investigators at present favor the view that the constriction of the vessels is merely an accompaniment of the graver effects on the ganglionic structures.

In dogs quinine and several of the synthetic compounds of the series have been found to exert a deleterious action upon the eyes. The pupils are dilated and react sluggishly and there is some pallor of the disc but no marked change in the retinal vessels. The striking change is in the cells of the ganglionic layer of the retina, many of which are destroyed. There is also some edema of the retina. These changes are produced by quinine and by the synthetic drugs, ethylhydrocupreine, ethylapocupreine and isopropylapocupreine. On the other hand, the closely related hydroxyethylapocupreine given in comparable doses was not found to have any such effect upon the retinas of any of the animals.

The symptoms in the **ear** have generally been regarded as the result of congestion and hemorrhages in the tympanum and labyrinth, but Wittmaack has shown that degenerative changes occur in the spiral ganglion in the cochlea exactly analogous to those described in the retina. When quinine is taken continuously as a prophylactic, it is said to impair the hearing and sight permanently in some cases.

Quinine possesses some irritant action which betrays itself in discomfort in the stomach and eructation after large and repeated doses by mouth, and by pain and tenderness when it is injected subcutaneously.

Large doses of quinine produce some confusion and depression with a sense of fullness and heaviness in the head from their action on the **Cerebrum**, and this is sometimes accompanied by uncertain gait and slow pulse. Very few cases of fatal poisoning have been satisfactorily

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determined to be due to quinine, although a considerably larger number have been attributed to it. In these cases marked weakness of the heart and collapse accompanied by loss of sight and hearing, muscular weakness, apathy, slow gasping respiration and finally unconsciousness and total failure of the respiration were observed. In some cases delirium and convulsions have been noted. Enormous doses of quinine sulfate have been swallowed without any serious results. Thus in one case 30 grams (1 ounce) produced only some confusion and noises in the ears. In general, however, symptoms of poisoning occur when the concentration of the drug in the blood exceeds 0.01 per cent.

The extensive use of quinine in therapeutics has demonstrated that many persons have curious **Idiosyncrasies** in regard to it. This is betrayed in many cases by the development of ear symptoms after comparatively small doses, but in others symptoms arise which do not appear in the great majority of people even after large doses. The commonest of these are skin eruptions, of which a large variety have been described, and which can be distinguished from ordinary diseases of the skin only by the history, or by the detection of quinine in the urine, or by a positive reaction to a quinine solution when it is applied to a scratch in the skin. These exanthemata are often accompanied by some rise in temperature, which has received more attention than it appears to deserve, for it is rare and, even when present, is of insignificant extent. Other less important effects, which have been noted, are dyspnea, gastric discomfort, vomiting and diarrhea. Patients with an idiosyncrasy to quinine sometimes exhibit abnormal reactions to other alkaloids of this group. This is not always the case, as malarial patients who have been unable to take quinine on account of its unpleasant effects upon them have been successfully treated with quinidine. In some cases the administration of quinine is followed by fever and hemoglobinuria (black water) or albuminuria. The exact relation between quinine and this condition is a matter of dispute; blackwater fever occurs occasionally in sufferers from old malarial infection when no quinine has been given, but in many cases the symptom is provoked only by quinine; on the other hand it often passes off when the treatment is continued. Quinine has no hemolytic action except in quantities which would prove immediately fatal, and the blood of these blackwater patients is not more readily laked by it than normal blood.

The **Uterus** is aroused to contraction by quinine, and abortion occurs occasionally after its use in malaria, while in other cases labor pains may be induced.

The **Blood** often contains fewer leucocytes after quinine in man and in animals. According to Roth, a single dose generally causes leucocytosis at first, perhaps arising from contraction of the spleen. This is followed by a fall in the number of white corpuscles, especially of the lymphocytes, though the polynuclear cells are also reduced. The polynuclears then increase in number until a distinct leucocytosis is again present, but the lymphocytes remain reduced in number, while in the preliminary leucocytosis they predominate. Hemolysis occurs only

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when quinine is present to the amount of 0.5 per cent, which is more than sufficient to arrest the heart.

The **Spleen** undergoes a marked diminution in size (Roth), presumably from active contraction of its muscular fibers. A similar constriction has been observed in the bronchi in animals.

The **Metabolism** is not affected by quinine in ordinary doses, the excretion of carbon dioxide and the absorption of oxygen remaining unchanged. Experiments have failed to show any alteration in the protein metabolism either in man or animals under treatment with large doses of quinine.

Temperature.—Quinine has no significant effect on the normal temperature in man or in animals; it may reduce it by 0.1 to 0.2 degrees in some cases, while in others its use is followed by a rise of similar dimensions. Its specific effects in preventing the rise of temperature in malaria are due to its destroying the parasite and not to any direct action on the mechanism which controls the temperature; until the parasite is destroyed, quinine is unable to reduce the body heat or even to prevent its rising. In other forms of fever, quinine usually fails to reduce the temperature in man, though it is sometimes successful in doing so. In animals large doses are found to lower fever temperature, but this is often accompanied by such symptoms as depression and muscular weakness, which in themselves would reduce the amount of heat formed and thus lower the unstable fever temperature.

Excretion.—Quinine appears in the urine within a short time (fifteen minutes) after its exhibition by the mouth, and it continues to be excreted by the kidney in some quantity during the next twenty-four hours, and in smaller amounts up to about seventy-two hours. Only about one-third of that absorbed appears in the urine, however, and only traces have been found in the other excretions, so that two-thirds or more undergoes complete destruction in the tissues. When quinine is injected into the subcutaneous tissues, some of it is deposited locally and only slowly redissolved, so that traces may be found in the urine for a week or more. When it is injected into the blood, it leaves the plasma within a few minutes, becoming attached to the corpuscles either by a process of adsorption or by forming some firm combination from which it is difficult to liberate it. It does not accumulate in any of the organs to any significant extent although small quantities have been found in the lungs, liver, heart, kidneys, and brain during the first two hours after the drug has been given intravenously.

It is sometimes stated that a **tolerance** to quinine may be acquired by prolonged treatment, but this seems to be incorrect, the same symptoms occurring and the same amount appearing in the urine after prolonged administrat on.

Of the other cinchona alkaloids, **quinidine** resembles quinine closely in most respects. It is employed for its effects on the heart, which appear to be similar in character to those of quinine, but are five to ten times more powerful. Because of its therapeutic importance, it will be discussed at greater length in the next section.

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Cinchonine, while very similar to quinine in most points, has some tendency to produce convulsions, but this effect is much more liable to occur under **Cinchonidine**, which, save for its resemblance in other features to quinine, would be entitled to be classed among the convulsive poisons. These convulsions are of an epileptiform character, and are only produced by very large doses, but even small quantities administered to epileptics have been said to increase the number of the attacks. These epileptiform seizures are not prevented by the removal of the cerebral cortex in dogs, and the irritability of the motor areas is not altered by cinchonidine, so that some lower division of the central nervous axis appears to be the seat of action in these animals; but in man the more highly developed cerebral cortex is also involved. Different species of animals apparently differ in respect to their susceptibility to the convulsive action of the cinchona alkaloids, rats and mice rarely or never showing convulsions. Even in other species which are susceptible in this respect the doses of the more common cinchona alkaloids necessary to produce convulsions approach very nearly amounts which would prove lethal. **Cinchonamine** possesses an even more marked convulsant action than cinchonidine.

The effects of the other alkaloids have not been the subject of much investigation, but they seem to differ from quinine chiefly in their effects on the central nervous system. These are not entirely absent in quinine itself, for, as has been stated already, the reflex irritability is at first increased and then diminished in both frogs and mammals, and in some cases even convulsions are stated to have occurred in quinine poisoning.

Many synthetic derivatives have been formed from the cinchona alkaloids, but few of them have been examined pharmacologically. *Optochin* or *ethylhydrocupreine*, one of these derivatives, differs from quinine by the presence of an ethoxyl instead of a methoxy group in the cupreine nucleus. It was introduced by Morgenroth for the treatment of pneumonia but is liable to cause blindness and no longer has a place in therapeutics. *Cupreine*, which is obtained from *Remijia* and its ethyl derivative have also been used experimentally but are too toxic for therapeutic use.

Therapeutic Uses.—The introduction of cinchona into therapeutics was due to the discovery of its efficacy in ague or **Malaria**, and until the introduction of the recent chemotherapeutic agents, the action of quinine in malaria was quoted as the best example of a specific in therapeutics. The explanation of its action was only reached when Laveran discovered the parasites of malaria, although in 1868 Binz suggested that the then unknown malarial poison was probably rendered inert by quinine. Malaria may be due to four distinct protozoa of the genus **Plasmodium**, the clinical course of the disease varying with the different infecting organisms. Infestation with *Plasmodium vivax* causes **benign tertian** or **vivax** malaria; *Plasmodium falciparum* induces **malignant tertian**, subtertian or estivo-autumnal malaria; *Plasmodium malariæ* gives rise to **quartan** malaria and *Plasmodium ovale*, the rarest of all, causes **ovale** malaria.

Malaria is an acute and chronic disorder characterized by fever, anemia and splenomegaly. The life cycle of the parasites responsible for the disease consists of a sexual phase **(sporogony)** during which multiplication takes place in certain anopheline mosquitoes and an asexual phase **(schizogony)** with multiplication in the human host. The latter process involves asexual multiplication of the parasite in the infected erythrocyte as well as the formation of male and female gametocytes which do not multiply in man but which infect the mosquito.

The parasites enter the red-blood corpuscles and multiply there,

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and then, issuing from the cells in immense numbers, invade new corpuscles. When the spores break out of the red cells, there is a sharp attack of fever, which passes off when they have reached the interior of new corpuscles, but returns when a new swarm of spores is liberated. The fever thus recurs at regular intervals in the simpler forms of malaria, but may be rendered irregular by double or multiple infections. The parasites of malaria belong to the group of the protozoa and are thus nearly related to the ameba on which Binz made his original observations.

The organisms of malaria are most susceptible to quinine when they are in the free state in the plasma, though the less dangerous forms are also destroyed after they have reached the shelter of the corpuscles. In the more malignant form of infection, the parasites in the corpuscles are apparently not affected by quinine and can only be got rid of by preventing them from being reinforced by new broods. It is therefore of the first importance to supply quinine to the blood at the period at which the spores are liberated. When quinine is given at the appropriate time, the organism breaks up and disappears, but a few more resistant forms may escape and multiply until they are numerous enough to provoke another paroxysm of fever; the treatment should therefore be continued until all the parasites have succumbed.

In a drop of malarial blood the plasmodia may be seen in active movement, but a minute drop of quinine solution paralyzes and kills them, exactly as it kills the common protozoa found in water, the only difference being that the malarial organism is infinitely more susceptible to its action. The malarial organism appears to be acted on specifically by quinine, that is, more strongly than other living cells, and the alkaloid can consequently be introduced into the human body with impunity in doses which are destructive to the simpler organisms which have invaded it. Experience has shown that quinine is most effective when it can act during and immediately after the paroxysms, and this is now explained by the fact that the organisms are in their least resistant form—the ameboid—at this time. If quinine is given three or four hours before an attack, sufficient will remain in the blood when the temperature begins to fall to destroy the unprotected spores of the parasite, or the same result may be obtained by a dose given as the temperature begins to fall, provided the drug is rapidly absorbed, as is ordinarily the case.

Preparations.—The cinchona alkaloids are available in a number of preparations. Quinine is used in the form of its salts of which the sulfate and the dihydrochloride are the best known and are in general preferred.

A mixture of cinchona alkaloids is also available for the treatment of malaria under the name of *Totaquine*. It is prepared from suitable species of Cinchona and contains not less than 70 per cent of crystallizable alkaloids of which not less than one-fifth is quinine. This preparation was originally recommended by the Health Committee of the League of Nations for the treatment of malaria where the high cost of quinine makes the wide use of the pure alkaloids impracticable. During the Second World War the limited supply of quinine made necessary the use of Totaquine and led to its official pharmacopeial recognition. It is used in the same dosage as quinine. A second preparation of the

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mixed alkaloids of cinchona is *Quinetum*. This consists of equal parts of quinine, cinchonidine and cinchonine, that being approximately the normal proportion of these alkaloids in *Cinchona succirubra*.

For children quinine tannate or quinine ethylcarbonate (equinine) which are insoluble and hence tasteless salts may be employed.

In cases of sensitiveness to quinine, quinacrine (atabrine) may be substituted and in fact this drug as shown in a later section is preferred to quinine in the suppressive treatment of malaria as well as in the treatment of infections due to Plasmodium falciparum. In some cases small doses of quinine may be followed by severe effects on the hearing; in these cases bromide often relieves the symptoms when given in adequate doses. In pregnancy quinacrine (atabrine) is preferred to quinine since the latter drug is less apt to induce abortion.

Although quinine, as already stated, was long the mainstay of treatment of malaria, the loss of the principal source of supplies of the drug during the Second World War and the epidemiologic importance of malaria in the Pacific areas of combat led to the search for new and the reëvaluation of other available antimalarials. As a result of these studies quinacrine (atabrine) displaced quinine as the principal antimalarial in general use. The chief usefulness of quinine is in the treatment of benign tertian (vivax) malaria in which its effectiveness is equal if not greater than that of quinacrine.

Dosage and Method of Administration.—Quinine is rapidly absorbed from the gastro-intestinal tract and hence whenever possible it is administered by this route in gelatin capsules to avoid its bitter taste. However, occasionally when profuse and continuous vomiting makes oral administration impossible, and in comatose patients, or those ill with severe complications, it may be necessary to initiate treatment by parenteral therapy. This method of administration should be superseded as early as practicable by oral administration. When administered parenterally, quinine dihydrochloride is given intravenously in doses of 0.6 gram (10 gr.) dissolved in 300 to 400 cc. of sterile physiologic saline. It should be injected very slowly with attention to a rising pulse rate or fall in blood-pressure which are indicative of impending reaction. The drug is eliminated in about three hours and hence the treatment must be repeated after three to four hours unless superseded by the oral route of administration at this time.

In the treatment of clinical malaria, quinine sulfate is administered orally in doses of 1 gram (15 gr.) three times a day after meals for two days followed by 0.6 gram (10 gr.) three times a day after meals for five days. This gives a total dose of 15 grams (225 gr.) in seven days.

For the suppressive treatment of malaria, quinine is administered where possible for at least two weeks prior to the expected exposure in doses of 0.6 gram (10 gr.) daily with the evening meal. However, quinacrine is more effective as a prophylactic against malignant tertian malaria.

Quinine was also used formerly in other febrile conditions and in the treatment of neuralgia and headache but has been replaced by the more effective bactericides and analgesics now available. The practice of

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administering quinine or other antimalarial drugs in all fevers in a malarious area before demonstration of the parasite is to be deprecated. Examination of the blood is necessary not only to determine the presence of malaria but also to determine the species of the infecting parasite and the drug of choice in a given case.

The tinctures of cinchona are often prescribed as **Stomachic Bitters,** and for this purpose may be fortified by preparations of nux vomica or of the simple bitters.

Quinine in combination with castor oil is used as an ecbolic to increase the contractions of the uterus during labor or more commonly to initiate labor. Its action as an ecbolic is feeble and in no way comparable to that of such potent ecbolics as the ergot alkaloids or posterior pituitary liquid.

Quinine in combination with urea has also been used as a **local anesthetic,** but it is far inferior to the synthetic local anesthetics (p. 411) for this purpose. It differs from cocaine in inducing anesthesia more slowly and still more in maintaining it for many hours or even days. It has been advised to wash painful wounds after operation, to relieve after-pains, to spray the throat and for many other purposes. Its toxicity after absorption is very low, but it injures the tissues locally and delays healing.

A 5 per cent solution of quinine and urea hydrochloride is used as a sclerosing agent in internal hemorrhoids. However, the treatment is not without its drawbacks as complications such as hemorrhage, ulceration and stricture of the rectum may follow, and other sclerosing agents such as morrhuic acid have replaced it for this purpose.

Preparations

U. S. P.

Quininæ Sulfas, quinine sulfate, white needle-like crystals. Dose, 0.6 gram.

Quininæ Bisulfas, quinine bisulfate, white crystals. Dose, 1 gram.

Quininæ Æthylcarbonas, quinine ethylcarbonate, euquinine, is only slightly soluble in water and is practically tasteless. Dose, 1 gram.

Quininæ Hydrochloridum, quinine dihydrochloride, a white powder soluble in water. Dose, 1 gram.

Quininæ et Ureæ Hydrochloridum, quinine and urea hydrochloride, contains about 58 per cent of quinine. It is very soluble in water.

Quininæ Hydrochloridum, quinine hydrochloride, white silky needles. Dose, 0.2 gram.

Injectio Quininæ Hydrochloridi et Æthylis Carbamatis, quinine hydrochloride and ethyl carbamate injection.

Totaquina, totaquine, a mixture of cinchona alkaloids. Dose, 0.6 gram.

Tabellæ Totaquinæ, totaquine tablets. Dose, 0.6 gram.

B. P.

Cinchona, the bark of various species of cinchona trees containing at least 6 per cent of the alkaloids of cinchona. Dose, 0.3 to 1 gram.

Extractum Cinchonæ. Dose, 0.12 to 0.5 gram.

Extractum Cinchonæ Liquidum contains 5 per cent of the alkaloids of cinchona. Dose, 0.3 to 1 mil.

Tinctura Cinchonæ contains 1 per cent of the alkaloids of cinchona. Dose, 2 to 4 mil.

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TINCTURA CINCHONÆ COMPOSITA contains 0.5 per cent of the alkaloids of cinchona, also orange peel, serpentary and cochineal. Dose, 2 to 4 mil.

TINCTURA CINCHONÆ COMPOSITA CONCENTRATA, concentrated compound tincture of cinchona. Dose, 0.5 to 1 mil.

QUININÆ BISULPHAS. Dose, 0.06 to 0.6 gram.

TABELLÆ QUININÆ BISULPHATIS. Dose, 0.06 to 0.6 gram.

QUININÆ DIHYDROCHLORIDUM. Dose, 0.06 to 0.6 gram.

QUININÆ ET ÆTHYLIS CARBONAS, euquinine. Dose, 0.1 to 1 gram.

QUININÆ HYDROCHLORIDUM. Dose, 0.06 to 0.6 gram.

TABELLÆ QUININÆ HYDROCHLORIDI. Dose, 0.06 to 0.6 gram.

QUININÆ SULPHAS. Dose, 0.06 to 0.6 gram.

QUININÆ TANNAS contains about 33 per cent of quinine. Dose, 0.1 to 1 gram.

TOTAQUINA, a mixture of alkaloids from various species of cinchona, containing not less than 70 per cent of crystallizable alkaloids with not less than one-fifth of quinine. Dose, 0.06 to 0.6 gram.

LIQUOR QUININÆ AMMONIATUS, ammoniated solution of quinine, contains 2 per cent of quinine sulfate. Dose, 2 to 4 mil.

SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA, Easton's syrup. Dose, 2 to 4 mil.

INJECTIO QUININÆ ET URETHANI. Dose, 0.5 to 5 mil. by intravenous injection as a sclerosing agent.

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II. QUINIDINE

Quinidine which has the same formula as quinine, being an optical isomer of the latter, is used in the form of its sulfate as a cardiac depressant to combat exaggerated excitability of the heart muscle as seen in auricular fibrillation and flutter, extrasystoles, tachycardia or other forms of heterotopic rhythm. Wenckebach in 1914 first called attention to the effect of the cinchona derivatives on cardiac rhythm. One of his patients had noted that the ingestion of quinine relieved the attacks of paroxysmal auricular fibrillation from which he occasionally suffered. Frey in 1918, studied the matter further and showed that of the cinchona alkaloids, quinidine was most effective. The mechanism of action of these drugs in modifying cardiac rhythm, as well as the functional significance of the observed arrhythmias was not clearly understood at

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this time. Hence, quinidine was used indiscriminately for a time in the treatment of arrhythmias generally with dire consequences in some cases. This led to its being discarded as a dangerous drug. At present, the indications for the use of quinidine are clearly definable and it has resumed its place in the therapeutics of certain types of arrhythmias.

Mechanism of Action.—Quinidine, like quinine, is a general protoplasmic poison and like the latter is a depressant of skeletal and cardiac muscle. Quinidine prolongs the refractory period of cardiac muscle, being much more effective in this respect than quinine. Quinidine also reduces the excitability of the heart, this action affecting both the auricles and the ventricles. As a consequence of this action, the rate of the heart is slowed. The action of quinidine is directly upon the heart muscle and not through the vagus; hence it is not abolished by atropine. The site of action of quinidine is both on the sino-auricular node and on the conduction bundles between the auricle and ventricle. Large doses of the drug may thus cause arrest of the heart by depressing the sino-auricular node or by causing an auriculoventricular block through action on the bundle of His.

Quinidine thus differs fundamentally from digitalis in its action on the heart. The therapeutic value of the latter, as we have seen, depends primarily on its effect on the tone and contractility of the myocardium. Quinidine, on the other hand, merely reduces the number of stimuli which arise and the rapidity with which these stimuli are conducted through the heart without improving the force of its contraction. Both drugs may slow the heart and abolish fibrillation but since the mechanism by which these effects are accomplished differ, it is readily seen why the indications for the use of the two drugs are not the same.

Therapeutic Use.—Quinidine sulfate is used in conditions in which the primary disturbance in the heart is due to an increased excitability or to the presence of a focus of ectopic stimuli. Such conditions are encountered clinically in paroxysmal auricular fibrillation, in auricular flutter and in paroxysmal tachycardia. Auricular fibrillation is most commonly observed in rheumatic heart disease. However, the primary disorder in this case is not the arrhythmia which is present but the myocardial dilatation and insufficiency. Hence digitalis is the drug of choice in this condition, since this drug actually increases the cardiac output without arresting the fibrillation of the auricle. Quinidine, on the other hand, is contraindicated in this condition since not only does it fail to improve the function of the heart by increasing its output, but by restoring the normal auricular contraction the mural thrombi present in the auricles may be dislodged and result in fatal embolism.

On the other hand, in **paroxysmal auricular fibrillation** or **flutter**, in which there is no evidence of cardiac damage and in which the abnormality of rhythm is of recent origin, quinidine is used to restore the normal cardiac rhythm. Likewise in **paroxysmal tachycardia** the symptoms of complaint are due to the abnormal rate of the heart. By reducing the excitability of the cardiac muscle, quinidine reduces the rate of the heart and thus induces its therapeutic effects.

In the treatment of **paroxysmal auricular tachycardia**, quinidine is less

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effective. In this condition a series of rapid intermittent discharges arising from an abnormal focus in the auricle induce a tachycardia with a regular pulse rate of 150 to 200 or more per minute. This condition is often terminated by application of pressure to the carotid sinus, by inducing vagal activity by pressure on the eyeballs, respiratory exercises, or the use of syrup of ipecac as an emetic. Should these measures fail, β-methylacetylcholine, quinidine, or digitalis may be used. For the prevention of recurrences, digitalis or quinidine are indicated.

In **paroxysmal auricular flutter** there is a circus movement which exists at a rate of about 350 per minute in the auricular tissue between the superior and inferior vena cava. This is transmitted to the ventricle which beats at half this rate, that is, at 175 per minute. Quinidine administered in this condition lengthens the refractory time of the muscle thus terminating the circus movement. If this fails, digitalis is indicated. Quinidine is also used to prevent recurrences of attacks of auricular flutter.

Paroxysmal auricular fibrillation is also effectively terminated by quinidine. However, the use of this drug in this condition is limited since in most cases the condition is of long standing and associated with heart failure for which digitalis is indicated. Only when the paroxysms of fibrillation are of less than a week in duration and where there is no evidence of valvular lesions should quinidine be used.

In **ventricular tachycardia,** a rapid series of intermittent discharges arise in the ventricle giving it a rate of 100 to 250 per minute. The condition is usually associated with myocardial disease and may be seen, for example, as a complication following coronary thrombosis. Quinidine is the drug of choice in this condition although care must be taken that the intraventricular conduction not be unduly prolonged, particularly when large doses of the drug are used. The use of quinidine is dangerous in the presence of auriculoventricular block and the existence of this condition should be excluded before using it to abolish ventricular tachycardia. The routine use of quinidine as a prophylactic against the development of ventricular tachycardia following coronary thrombosis is not desirable but the drug is of value in such patients as manifest premature ventricular contractions in order to prevent the establishment of paroxysmal ventricular tachycardia which may proceed to a fatal fibrillation.

In **sinus tachycardia** quinidine either does not affect the rate of the heart or actually increases it.

Dosage.—Certain individuals manifest an idiosyncrasy to quinidine and hence the drug is usually given in a preliminary test dose of 0.2 gram (3 gr.) orally which may be repeated after two hours in order to detect any undue susceptibility to the drug. If no unpleasant symptoms arise, doses of 0.2 to 0.4 gram (3 to 6 gr.) are given three to five times daily for one to three days. In some cases of paroxysmal auricular tachycardia, auricular fibrillation or ventricular tachycardia, 0.6 gram (10 gr.) every two hours for 3 to 5 doses may be necessary to terminate the attack. For the prevention of recurrences of fibrillation or flutter, doses of 0.3 gram (5 gr.) three times a day are

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used, this dose being progressively increased if necessary until the desired response is elicited.

Dihydroquinidine occurs in commercial quinidine sulfate usually to the extent of about 20 per cent. The results usually attributed to quinidine are thus actually the combined effects of it plus its dihydro derivative. Pure dihydroquinidine is about 18 per cent more toxic than quinidine. On the other hand, it is more potent than pure quinidine or commercial quinidine sulfate against fibrillation of the heart. The pure drug has as yet not been used clinically.

PREPARATIONS

U. S. P.

QUINIDINÆ SULFAS, quinidine sulfate, white crystals, only slightly soluble in water. Dose, 0.2 gram.

TABELLÆ QUINIDINÆ SULFATIS, quinidine sulfate tablets. Dose, 0.2 gram.

B. P.

QUINIDINÆ SULPHAS. Dose, 0.2 to 0.6 gram.

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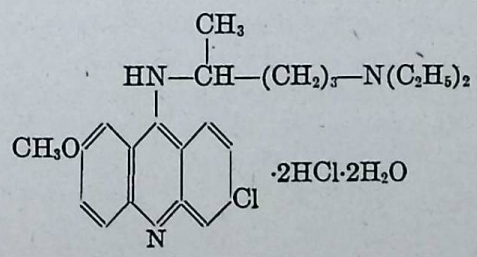
III. QUINACRINE (MEPACRINE, ATABRINE)

This important drug, first synthesized by Mietsch and Mauss, was introduced by Kikuth under the name atebrine (atabrine) as a substitute for quinine in the treatment of malaria. Experimentally, quinacrine was found to be highly effective in treating the malaria of monkeys and birds, being more effective in this respect than quinine. Experience in the Second World War showed its value and superiority in certain



respects over quinine. As seen in the accompanying formula it is unrelated to quinine chemically but is the dihydrochloride of an alkyl-

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amino-acridine derivative. It is a bright yellow crystalline powder, slightly soluble in water, forming a neutral fluorescent solution.

Absorption and Excretion.—Although promptly absorbed from the intestinal tract following its administration orally, quinacrine is less rapidly absorbed than quinine. Moreover, since it is stored in the tissues the maximum blood level on a constant intake of the drug is only gradually attained due to the gradual saturation of the tissues. Thus on a dosage level of 0.1 gram (1½ gr.), daily, only half the maximum blood level attainable is reached in the course of a week. The maximum level is attained only at the end of the fourth week. A similar rate of decline follows withdrawal of the drug, so that two to four weeks must elapse before it entirely disappears from the body. There is also a great variability in the plasma level attained in different individuals receiving the same dose of the drug.

The presence of quinacrine in the tissues is manifested by a bright yellow discoloration seen in the skin, as well as in the internal organs of the body. It is excreted in the urine, imparting to it a deep yellow color on acidification, and in the sweat, staining the clothing. The discoloration of the skin disappears within a few days or weeks following cessation of the drug depending upon the dose and duration of treatment.

Toxicity.—Quinacrine is relatively non-toxic in therapeutic doses. Long continued use of the drug for more than a year has not resulted in any apparent ill-effects. There is no evidence that it exerts a toxic effect on the liver, although large doses in cats, is said to produce fatty degeneration of the liver and kidneys. The minimal lethal dose for cats is about 0.1 gram per kilo, while rabbits tolerate such amounts without apparent injury.

In man the toxicity of quinacrine is low and there seems to be a fairly wide margin of safety, but symptoms of intolerance have been reported, such as nausea and vomiting, gastric uneasiness and even acute abdominal pain, diarrhea, and headache. These symptoms are never serious and may soon disappear even with continued administration of the drug. Less than 1 per cent of individuals show a persistent intolerance to the drug. By commencing therapy with an initially small dose undesirable reactions are avoided. In some patients there has been a feeling of profound depression which has lasted for several days after the drug has been stopped and in certain cases the mental symptoms have approached those of a definite psychosis.

The incidence of **toxic psychosis** following quinacrine is about 1 in every 2,000 patients treated with the drug (Gaskell and Fitzhugh). This psychosis may begin either during the course of therapy or shortly after its conclusion. No specific therapeutic measures have been found useful in treating this psychosis except for the symptomatic treatment with sedatives, restraint and nursing care. Whether the psychotic episode is due to toxic reaction to the drug or is a result of the combination of the malaria plus the drug is undetermined, but the latter seems most probable.

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Skin rashes and other allergic manifestations are only rarely observed.

Therapeutic Use.—Although no drug is known which will entirely prevent malarial infections, quinacrine (atabrine) or quinine taken regularly in ample dosage will suppress the onset of symptoms of the disease. Their use for this purpose is designated as **suppressive therapy.** Although most infected individuals will become acutely ill with malaria following the discontinuance of suppressive treatment, a high proportion of infections with **Plasmodium falciparum** will not become clinically active following suppressive treatment with quinacrine (atabrine). Prolonged exposure to this drug does not increase the resistance of the parasite and hence clinical attacks occurring during or after suppressive treatment will respond promptly to further treatment. In general, attacks of malaria will occur within two to four weeks following the cessation of suppressive treatment but the disease may remain latent and appear months after the drug has been discontinued.

In the suppressive treatment of malaria, quinacrine (atabrine) is considered to be the drug of choice. For this purpose one tablet (0.1 gram, 1½ gr.) is given daily after the evening meal. In the rare instances of intolerance to atabrine, quinine in doses of 0.6 gram (10 gr.) daily may be substituted.

Quinacrine hydrochloride (mepacrine) is effective in destroying the asexual forms (trophozoites) of the Plasmodium. Its effectiveness against *Plasmodium falciparum,* the causative agent of malignant subtertian malaria, was shown during the recent war to be greater than quinine. It is equally as effective as quinine in benign tertian (P. vivax) and quartan malaria (P. malariæ). Quinacrine is also effective in blackwater fever where the use of quinine is contraindicated.

In treating clinical malaria, 0.2 gram (3 gr.) of quinacrine and 1 gram (15 gr.) of sodium bicarbonate, are administered by mouth with 200 to 300 cc. of sweetened fruit juices, tea, or water. This should be repeated every six hours for 5 doses. Thereafter, 0.1 gram (1½ gr.) is given three times daily after meals, for six days. This gives a total dosage of 2.8 grams in seven days.

The parenteral administration of quinacrine should be restricted to cases with severe complications such as vomiting, coma, or hyperpyrexia in which oral administration is difficult or impossible. When thus given the dihydrochloride is administered in doses of 0.2 gram (3 gr.) dissolved in 5 cc. of sterile distilled water. This solution is injected intramuscularly into each buttock, to give a total dose of 0.4 gram (6 gr.). An effective concentration in the blood is attained within fifteen minutes and maintained for about six hours.

If necessary, one or two additional doses may be given at intervals of six to eight hours with oral therapy initiated as soon as practicable. A total dose of 1.3 gram (20 gr.) by both routes in the first forty-eight hours is desirable after which the dose should be 0.1 gram three times daily after meals for five days (total 2.8 grams in seven days).

Quinacrine is also available in the form of its methyl sulfonate which is official in the British Pharmacopeia and which is used for parenteral administration instead of the dihydrochloride.

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PREPARATIONS

U. S. P.

QUINACRINÆ HYDROCHLORIDUM, quinacrine hydrochloride, mepacrine hydrochloride, a bright yellow crystalline powder. Dose, 0.1 gram.

TABELLÆ QUINACRINÆ HYDROCHLORIDI, quinacrine hydrochloride tablets. Dose, 0.1 gram.

B. P.

MEPACRINÆ HYDROCHLORIDUM, atabrin, quinacrine. Dose, 0.05 to 0.1 gram.

TABELLÆ MEPACRINÆ HYDROCHLORIDI. Dose, 0.05 to 0.1 gram.

MEPACRINÆ METHANOSULPHONAS, atebrin musonat, quinacrine soluble. Dose, 0.05 to 0.1 gram.

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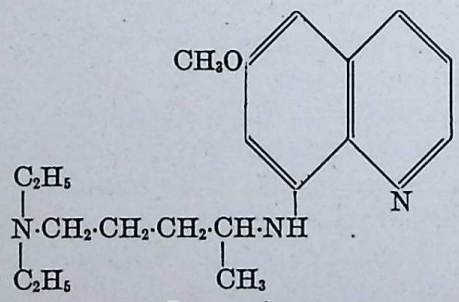
IV. PAMAQUINE (PLASMOCHIN, PLASMOQUINE)

This synthetic compound was introduced by Mühlens in 1926 as a substitute for quinine in the treatment of malaria. It is *N*-diethylamino-isopentyl-8-amino-6-methoxy-quinoline and as seen in the accompanying formula, is not a derivative of quinine but is somewhat distantly related to it. It is used in the form of the dihydrochloride or the official naphthoate. It was found to be quite effective against bird



Pamaquine

malaria and on that account was introduced into the treatment of malaria in man. Here it has been found to be quite active against the gametocytes and removes the crescents from the peripheral blood in a very short time. It renders the blood non-infective to mosquitoes thus preventing the transmission of malaria from one person to another. On the other hand, pamaquine has much less effect on the asexual form of parasites which are the cause of the clinical symptoms and which are very susceptible to quinine. On this account, pamaquine (plasmochin) was originally recommended for use in combination with quinine or at

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the completion of a course of treatment with quinacrine (atabrine). The drug was shown during the Second World War to be useless as a sole antimalarial agent.

Toxicity.—Pamaquine (plasmoquine) is a fairly toxic drug. In cats, doses of 2 to 3 mg. per kilo will produce methemoglobin formation. Injected intravenously into dogs and cats it is quite toxic to the heart, causing marked irregularities and heart-block together with depression of the heart and a fall in blood-pressure. Injected into normal cats and dogs, doses of from 5 to 7 mg. per kilo prove lethal; the symptoms consisting of dyspnea, cardiac irregularity, methemoglobinemia and asphyxia. Methemoglobin formation is one of the chief effects of the drug and is produced *in vitro* as well as *in vivo*.

The drug is disposed of rather slowly in the body; some is probably destroyed, while some is excreted in the urine.

In man the administration of pamaquine is frequently followed by epigastric pain, nausea, vomiting, headache, dizziness, and drowsiness, and by a certain degree of cyanosis. The appearance of cyanosis should be taken as a warning to discontinue the use of the drug. In mild cases this symptom is seen only in the fingers and lips but in severe poisoning the whole body may be discolored. The gastric distress is less if the drug is given after a meal.

In severe **intoxication** in man there is headache, dizziness, marked sweating and abdominal pain, which may be quite marked over the liver. Diarrhea and cyanosis may be present together with methemoglobinemia and methemoglobinuria. There may be jaundice and marked anemia and the patient may become drowsy and comatose. Anemia seems to predispose to the formation of methemoglobin, so that in cases of marked anemia the drug should be used very cautiously. In fact, on account of its toxicity the drug should never be given except under strict medical supervision, since the margin between the toxic and therapeutic dose is small.

Therapeutic Use.—Pamaquine, unlike quinine and quinacrine, has little effect on the trophozoites of *Plasmodia* and hence fails to control the clinical manifestations of malaria. There is some evidence to indicate that it tends to diminish the incidence of late recurrences of **vivax malaria** when used in conjunction with quinine or quinacrine. Its primary action, however, is on the gametocytes of *P. falciparum*.

Pamaquine is never used in the suppressive treatment of malaria.

In the treatment of vivax infections, the administration of 0.01 gram ($\frac{1}{6}$ gr.) of pamaquine hydrochloride or 0.02 gram ($\frac{1}{3}$ gr.) of its naphthoate with 1 gram (15 gr.) of sodium bicarbonate three times daily after meals concurrently with quinine lessens the likelihood of a relapse. Pamaquine, because of its toxicity is not given concurrently with quinacrine, but it may be given immediately following treatment with this drug or during the last days of treatment with quinine. When given in this way the dosages indicated above should be given for four days. These doses should be reduced for debilitated individuals.

Quinine, quinacrine (atabrine) and pamaquine (plasmochin), may all be combined in the following manner: quinine sulfate, 0.6 gram

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(10 gr.) given daily three times after meals, for from two to three days, or until the fever is controlled, followed by 0.1 gram ($1\frac{1}{2}$ gr.) of quinacrine (atabrine), three times daily with meals for five days, and after an interval of two days without medication, pamaquine (plasmochin) in doses of 0.01 gram ($\frac{1}{6}$ gr.) three times daily after meals for three to four days.

The wide experience gained in the Second World War in the treatment of malaria led to the establishment of quinacrine as the most important of the antimalarial drugs particularly because of its effectiveness in the suppression of falciparum infection. Pamaquine proved to be of little value.

PREPARATIONS

U. S. P.

PAMAQUINÆ NAPHTHOAS, pamaquine naphthoate, aminoquin naphthoate, the methylene-bis-β-hydroxynaphthoate of pamaquine, a yellow to orange yellow powder, insoluble in water. Dose, 20 mg.

B. P.

PAMAQUINUM. Dose, 0.025 to 0.05 gram.

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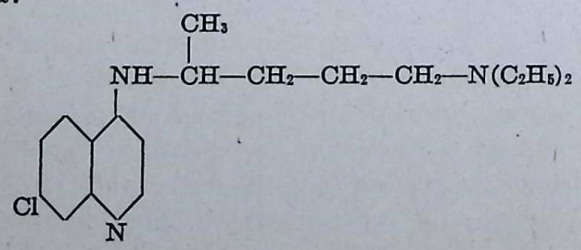
V. OTHER ANTIMALARIAL DRUGS

During the recent war, a great number of compounds related chemically to quinine, quinacrine, and pamaquine were synthesized and tested for their antimalarial action.

Several of those prepared were found to have advantages over the previously available drugs. Three of these may be referred to briefly here.

The compound originally designated by the code number **SN 7,618**, is 7-chloro-4(4-diethylamino-1-methylbutylamino) quinoline with the structural formula:



It has been marketed as the diphosphate, under the trade-name, Aralen but is officially designated as **chloroquine.** It appears to be an effective suppressive when administered no more frequently than once a week in a well tolerated dose, terminates abruptly clinical attacks of *vivax* malaria, and cures *falciparum* malaria when administered for several

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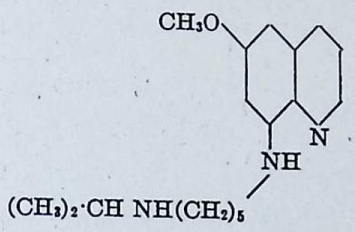
days. Unlike quinacrine, it does not discolor the skin nor does it cause any disagreeable gastro-intestinal symptoms. It is used in doses of 1.5 gram of the free base (equivalent to 2.5 grams of the diphosphate). An initial dose of 1 gram, followed by an additional 0.5 gram after six to eight hours, and a single dose of 0.5 gram on each of two consecutive days produces prompt disappearance of symptoms and of parasitemia. For suppressive therapy, a dose of 0.5 gram (0.83 gram of the diphosphate) once weekly is recommended.

Another antimalarial which has undergone experimental trial is **SN 13,276** (pentaquine) which, as may be noted from its accompanying formula, is related to pamaquine over which, however, it has several advantages, being more effective therapeutically and less toxic in the doses required clinically.



Paludrine, N′-*p*-chlorophenyl-N⁵-isopropyl-biguanide hydrochloride, has also been found to be non-toxic and more efficacious than mepacrine in the treatment of *tertian* malaria. It has been subjected to experimental studies by British investigators.

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S. EMETINE AND OTHER ANTIAMEBIC DRUGS

I. EMETINE (IPECACUANHA)

Ipecacuanha (ipecac), derived from the root of Cephaelis or Psychotria Ipecacuanha, has long been used for its emetic and expectorant virtues. The root contains from 2 to 3 per cent of total alkaloidal material which consists of Emetine ($C_{29}H_{40}O_4N_2$), Cephaline ($C_{28}H_{38}O_4N_2$), Psychotrine and others of less importance. Emetine as seen in the accompanying formula is a complex derivative of isoquinoline. It differs from cephaline by containing a methoxy (OCH_3) instead of a phenolic (OH) group and may be prepared from cephaline by methylation. Cephaline is obtained by reduction of psychotrine. Emetine and cephaline resemble each other in their action but the latter is ineffective as an expectorant while psychotrine is said to be almost inert.

Symptoms and Action.—When administered internally emetine has a bitter, acrid taste, and produces a copious salivary secretion, followed later by nausea and vomiting. The drug is generally largely eliminated by vomiting, so that no further effects are observed.

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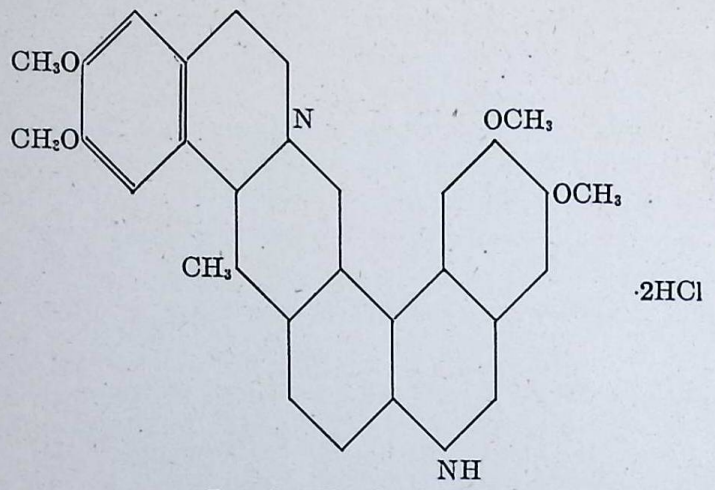
The nausea and vomiting are accompanied by the usual symptoms —muscular weakness and depression, increased secretion of saliva and of mucus by the glands of the throat and respiratory passages, often perspiration, and generally temporary acceleration of the pulse.



Emetine dihydrochloride

Quantities which are too small to provoke vomiting, induce prolonged nausea with increased mucous secretion along the respiratory passages, and some perspiration.

Emetine possesses a powerful **Local Irritant Action**, which is, however, much more marked in certain individuals than in others. The smallest quantity of the powdered root of ipecacuanha is sufficient to induce in the subjects of this idiosyncrasy considerable swelling and injection of the conjunctival and nasal mucous membranes, with salivation, tears, sneezing, coughing, and bronchial catarrh. When applied to the skin as a liniment, it produces redness, itching and occasionally a pustular eruption, but when injected hypodermically the alkaloids do not irritate the subcutaneous tissues.

The **emetic** action is mainly due to ipecacuanha irritating the stomach, and is thus a further example of its specific action on the mucous membranes. It is probable that there may be a further action on the medullary center when large quantities are injected intravenously in animals. but this is not involved in the ordinary methods of administration. If the action were due to the effects of the drug after absorption, vomiting would be caused by a smaller dose injected hypodermically or intravenously than is necessary by the mouth; but it is found that a dose of emetine sufficient to cause vomiting when swallowed, may be injected without any effects whatever. In the case of apomorphine, on the other hand, in which the action is central, the hypodermic emetic dose is smaller than that necessary when it is given by the mouth. The increased bronchial secretion, the perspiration, the acceleration of the pulse, and other attendant symptoms are similarly reflex in origin from the gastric irritation and do not indicate any direct action on the bronchi and other organs,

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When large doses are injected hypodermically, emetine induces nausea, vomiting, and purging, and blood is frequently voided in the stools, a condition of collapse follows, and the animal generally dies of exhaustion in the course of a few hours after the onset of the symptoms. Very large quantities injected subcutaneously or intravenously may fail to elicit vomiting, but the collapse symptoms appear, and after some weak convulsive movements, the animal dies of cardiac failure. In those cases in which death follows rapidly on the injection, no pathological lesions may be found after death, but in experiments where smaller quantities are injected, and the animal survives for eighteen to twenty-four hours, the stomach and intestine often exhibit the appearances of acute gastro-enteritis. The mucous membrane is swollen, congested, and often covered with a mucopurulent secretion or studded with ecchymoses, and in dogs ulceration is often present. A lesion which is not by any means constant, but which occurs in a considerable number of animals and especially in rabbits, is edema of the lungs. The heart changes are usually quite severe, animals surviving three or more days, showing necrosis of some fibers and degenerative swellings of the remaining muscle cells. These cardiac changes are apparently severe enough to be a cause of death.

The gastric and intestinal symptoms which follow from these large hypodermic doses suggest that emetine is excreted by the mucous membranes of the alimentary canal, and that it induces irritation and inflammation in the course of its excretion. In man, vomiting has followed the hypodermic injection of 4 grains of emetine, but 1 grain administered in this way has no such effect.

Emetine injected into a vein weakens the heart's action, and induces a fall of blood-pressure, but when it is injected subcutaneously or given by the mouth, the heart is not affected directly, but pathological changes in the muscle become apparent later.

In the frog emetine does not cause vomiting, but a slowly advancing central paralysis follows its injection, the spontaneous movements ceasing early, and later the reflex excitability disappearing. The contractions of the heart are rendered weak and irregular, and eventually cease from paralysis of the cardiac muscle.

Ipecacuanha has long enjoyed a reputation in one form of tropical dysentery, and the discovery that the cause of this form of dysentery was an ameba (Entameba histolytica) was soon followed by Roger's discovery that emetine has a specifically poisonous action on this parasite. This specific toxicity cannot be demonstrated in ordinary forms of ameba, nor in other protozoa, and even the entameba of dysentery is not strikingly susceptible to emetine when exposed to it in the test-tube; sometimes 1 per mille or even 1 per cent of emetine has not killed the ameba in the test-tube within an hour. On the other hand the effects in cases of dysentery treated with emetine are very satisfactory and the entameba disappears from the stools and tissues. The quantity of emetine that comes in contact with the parasite must be even smaller than that of quinine in cases of malaria, and the equivalent concentration is harmless to entameba outside the body. It is thus impossible to attribute the success of the treatment to a directly poisonous action on the parasite. Moreover, emetine fails to destroy the amebæ present in the lumen of the bowel but only acts on the parasites present in the tissues. The amebacidal action of the drug is apparently then not a direct one but requires the intermediation of the tissues of the host. Experimental work upon the treatment of cats infected with amebæ obtained from human sources have demonstrated that emetine will

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exert a beneficial action in such infections; apparently in such experiments the drug will act in the same way as in the natural disease in man.

Emetine and cephaline, the two chief alkaloids of ipecacuanha, resemble each other closely in their effects, cephaeline being somewhat more irritant than emetine. Ipecacuanha owes its action to the alkaloids, and differs from them only in acting more slowly and in having less tendency to cause purging, owing to its containing a large amount of tannin. The relative action of the two alkaloids in dysentery has not been accurately determined, but emetine is superior to cephaeline.

Therapeutic Uses.—Ipecacuanha has been largely employed as an **emetic**, and although it has been replaced for some purposes, notably in cases of poisoning, by apomorphine, it still has a certain field of usefulness in cases in which an emetic is indicated, but in which the hypodermic method is objectionable. At present ipecacuanha is used chiefly as an expectorant in the treatment of inflammatory conditions of the respiratory passages. For this purpose it is prescribed in smaller quantities than those necessary to produce emesis. It acts indirectly through its nauseating properties, and has the advantage that its action is much more prolonged than that of apomorphine. It increases the secretion of the bronchial mucous membrane, and further tends to render it more fluid, so that the mucus can be coughed up more easily. The increased secretion may also be of service by protecting the inflamed and irritable membrane from the cold air and thereby lessening the cough; opium is often added in order to further allay coughing by depressing the center, the well-known Dover's powder being a favorite prescription for this purpose. When the secretion of the bronchi is already excessive, and the cough is rather to be encouraged than repressed, these preparations are of course contraindicated.

Ipecacuanha is also employed as a **diaphoretic**, either alone or more commonly as Dover's powder. The perspiration is not so copious as that following pilocarpine and other sudorifics, but resembles rather that produced by warmth applied to the skin.

The principal therapeutic use of emetine is in the treatment of **amebiasis.** Ipecac or ipecacuanha root was formerly used in amebic dysentery, but very large quantities were required, and it was difficult to avoid nausea and vomiting. Opium and morphine were added for this purpose, and in addition the powder, made into pills, was enclosed in keratin or salol, which prevented it acting on the stomach, the pills being dissolved in the intestine, freeing the ipecac to exert its influence in that structure. But all these cumbrous methods have been rendered obsolete by the introduction of emetine into therapeutics. Rogers showed that the injection of the alkaloid is more efficient than the ipecacuanha treatment in amebic dysentery and in its sequelæ, hepatitis and hepatic abscess.

Amebiasis is due to the infestation of the colon by a pathogenic ameba, *Endamœba histolytica.* It is a widely prevalent disorder with an incidence which varies from about 4 to 20 per cent in the United States but may infest over 50 per cent of the population in tropical areas. The amebæ exist in a motile vegetative form (trophozoites) which invade

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the intestinal wall and which may enter the blood stream and give rise to abscesses usually in the liver but occasionally in the brain or other tissues. The amebæ are also found in the lumen of the gut as cysts in which form they are excreted and transmitted to new hosts. These encysted forms of the protozoa are found in convalescents from an acute attack of amebic dysentery as well as in those who manifest the disease in its asymptomatic form.

In the treatment of amebiasis, three classes of drugs are utilized: (1) emetine hydrochloride, (2) arsenic in the form of carbarsone and (3) some derivative of oxyquinoline.

Emetine is administered intramuscularly in the form of its hydrochloride. Subcutaneous injection is irritating and leads to the formation of painful indurations. In the treatment of acute amebic dysentery, emetine hydrochloride is administered once daily in a dosage not to exceed 1 mg. per kilogram of body weight per day over a period of seven to ten days in conjunction with carbarsone or preferably one of the oxyquinoline derivatives described below. In the treatment of amebic hepatitis and abscess of the liver, the intramuscular injection of emetine hydrochloride, as indicated above for ten days, is combined when necessary with aspiration or drainage of the abscess cavity.

Since emetine acts only on the parasites present in the tissues, it is not used in the treatment of chronic amebiasis. Moreover, because of its effects on the heart it should not be used in individuals manifesting evidence of myocardial disease.

The double salt emetine bismuth iodide has been recommended for oral administration particularly in chronic amebiasis but has little to recommend it.

Preparations

U. S. P.

Ipecacuanha, ipecac, the dried rhizomes of Cephaëlis ipecacuanha or of C. acuminata.

Fluidextractum Ipecacuanhæ, fluidextract of ipecac. Emetic dose, 0.5 cc.

Syrupus Ipecacuanhæ, syrup of ipecac. Emetic dose, 8 cc.

Emetinæ Hydrochloridum, emetine hydrochloride, a white or very slightly yellowish crystalline powder. Dose, 60 mg. daily, intramuscularly.

Injectio Emetinæ Hydrochloridi, emetine hydrochloride injection, a sterile solution in water. Dose, 60 mg., intramuscularly.

B. P.

Ipecacuanha, ipecacuanha root.

Ipecacuanha Pulverata, powdered ipecac. Dose, 0.03 to 0.12 gram; emetic dose, 1 to 2 grams.

Extractum Ipecacuanhæ Liquidum. Dose, 0.03 to 0.12 mil.; emetic dose, 0.6 to 2 mil.

Tinctura Ipecacuanhæ. Dose, 0.6 to 2 mil.; emetic dose, 15 to 30 mil.

Pulvis Ipecacuanhæ et Opii, Dover's powder. Dose, 0.3 to 0.6 gram.

Trochiscus Morphinæ et Ipecacuanhæ, each lozenge contains 0.002 gram morphine hydrochloride and 0.006 gram ipecac.

Emetinæ Hydrochloridum, emetine hydrochloride, the salt of the alkaloid obtained from ipecac. Dose, 0.03 to 0.06 gram.

Emetinæ et Bismuthi Iodidum, a complex iodide of emetine and bismuth. Dose, 0.06 to 0.2 gram.

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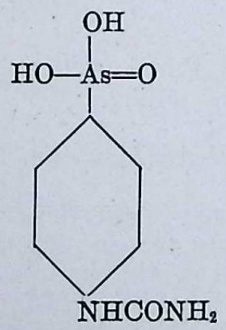
II. CARBARSONE

Following the success which attended the introduction of the organic arsenic compounds in the treatment of syphilis an attempt was made by Marchoux to employ these products in the therapeutics of amebiasis. For this purpose he used acetarsone (stovarsol), the acetyl derivative of amino-hydroxyphenyl-arsonic acid. Subsequently, treparsol was also used for the same purpose but this as well as acetarsone are only feebly amebacidal. The arsenical of choice in the treatment of amebiasis is Carbarsone, (4-carbaminophenyl-arsonic acid). This compound has shown itself to be superior to acetarsone, being less toxic and at the same time more actively amebacidal.



Carbarsone

Carbarsone is a white, almost odorless powder, very slightly soluble in water. It is administered orally in capsules containing 0.25 gram (4 gr.). The drug may also be given in a retention enema, 2 grams being dissolved in 200 cc. of a warm 2 per cent sodium bicarbonate solution. These enemata are given on alternate nights for 5 doses, the oral doses being omitted while the enemata are being employed.

Administered to animals in minimal lethal doses carbarsone produces symptoms of lethargy, loss of weight, abdominal distention and diarrhea. *Postmortem* examination shows renal necrosis with tubular degeneration. When doses within the therapeutic range are administered no toxic symptoms are observed and no tissue injury has been described. A possible toxic effect upon the optic nerve has to be considered, as the modified amino group in the molecule is in the para position in relation to the arsenic.

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The **excretion** of the drug has been studied in the human subject and it has been found to follow closely the excretion curve of acetarsone. The excretion in each case is rather slow and therefore there would appear to be a possibility of cumulative action of the drug if its use were continued over a prolonged period.

Although carbarsone appears to be a relatively non-toxic drug for use in amebiasis a few cases of poisoning have been reported. The symptoms were in one case a local dermatitis while others have shown diarrhea, localized edemas, and some visual disturbance. More commonly one observes abdominal distress, nausea, and vomiting, and rarely exfoliative dermatitis, but toxic reactions to the drug are rare.

Carbarsone not only acts on the protozoa present in the tissues but also on those present in the intestinal contents. However, despite its effectiveness as an amebacide it cannot be depended upon to eliminate the infection in all cases of acute amebiasis. For this reason it is given in doses of 0.25 gram (4 gr.) three times daily concurrently with emetine. On the other hand, the relatively asymptomatic cyst-passer may be treated by carbarsone alone. For this purpose 3 or 4 capsules each containing 0.25 gram (4 gr.) are administered orally three times daily for seven to ten days. After four to six weeks the stools are reëxamined for the presence of amebæ.

Carbarsone is contraindicated in patients manifesting liver or kidney disease.

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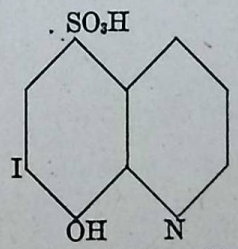
III. HYDROXYQUINOLINE DERIVATIVES

This group of amebacides are halogenated hydroxyquinoline derivatives. The principal ones in use are chiniofon, (quinoxyl), anayodin (yatren), vioform and diodoquin. They are efficient amebacides but their action is limited to the parasites present in the intestinal contents or on the surface of the intestinal mucosa, the parasites present in the tissues remaining unaffected. The drugs are used concurrently with emetine in the treatment of acute or active amebiasis, for prophylaxis, and for the control of carriers.

Chiniofon and diodoquin are contraindicated in cases of liver disease while none of this group should be used in patients suffering from severe kidney disease or those who manifest an idiosyncrasy to iodine.



Iodo-hydroxyquinolinesulfonic acid

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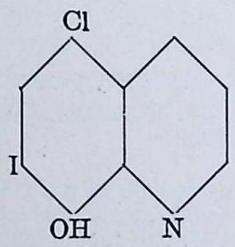
Chiniofon powder is a mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, its sodium salt and sodium bicarbonate. The free acid has also been employed for the treatment of amebiasis under the names yatren, loretin and anayodin.

Chiniofon is a yellow powder with a slight odor and a bitter taste. It dissolves in water with effervescence due to the reaction of the uncombined bicarbonate upon the acid. It is given to adults in doses of 0.25 to 1 gram three times daily or by enema 1 to 5 gram doses dissolved in 200 cc. of warm water. It may be used in the above dosage concurrently with emetine in the treatment of active amebiasis or in doses of 1 gram (10 gr.) three times a day for eight to ten days in the treatment of carriers.

Chiniofon causes diarrhea in a considerable percentage of cases, but aside from this disturbance, symptoms of intolerance seem to be rare. The drug is not as active an amebacide as is vioform, making large doses necessary.

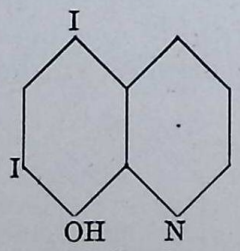
Vioform (7-iodo-5-chlor-8-hydroxyquinoline) is a grayish-yellow powder which was originally introduced as a substitute for iodoform and is used as a dusting powder for abrasions of the skin. Anderson and Koch discovered its amebacidal activity in monkeys and David, Johnstone, Reed and Leake first reported its use in human amebiasis.



Vioform

Vioform is administered in the form of enteric coated tablets or capsules. A course of therapy consists in the administration of 0.25 gram three or four times a day for ten days. At least a week or ten days should intervene between successive courses but it may be given in courses alternated with carbarsone. Like chiniofon it may also be given rectally. It is effective only in intestinal amebiasis and acts on both the motile and cystic forms of the ameba.

Vioform is also used in the treatment of **Trichomonas vaginalis vaginitis** for which purpose it is usually insufflated as a powder (diluted ten times with magnesium trisilicate) into the vagina.



Diodoquin

Diodoquin (5,7-diiodo-8-hydroxquinoline) differs from vioform in containing a second iodine atom in place of chlorine. It is the most

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recent of the halogenated hydroxyquinoline derivatives to be introduced for the treatment of amebiasis and preliminary studies indicate that it may prove superior to the older drugs. Diodoquin is relatively non-toxic, only headache occasionally following its use in therapeutic doses. It is administered in the form of tablets in doses of 0.6 gram (10 gr.) three times daily in conjunction with emetine. It has also been used alone for the treatment of active as well as asymptomatic cases, in which case it is given in the above-mentioned dosage for twenty days. This course of therapy must be repeated several times for complete eradication of the amebæ.

PREPARATIONS

B. P.

CHINIOFONUM, chiniofon, pulvis chiniofoni, a mixture of approximately four parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part by weight of sodium bicarbonate. Dose, 0.06 to 0.5 gram; rectally, 1 to 5 grams.

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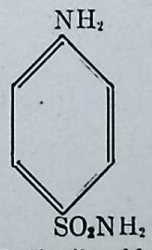
T. SULFANILAMIDE AND ITS DERIVATIVES

One of the most fascinating chapters in medical history has been written in recent years by the introduction of two important classes of chemotherapeutic agents—the sulfonamides and the antibiotics. These compounds have furnished the physician with potent specific remedies with which many previously highly fatal infections can be counteracted. Although specifics against protozoal diseases were available in quinine and salvarsan the sulfonamides were the first systemic anti-infectives which proved effective against bacterial diseases.



Sulfanilamide

Sulfanilamide, the parent substance of these derivatives was synthesized in 1908 by Gelmo and was widely used as an intermediary in the dye industry. Its virtues as a drug remained unknown although Heidel-

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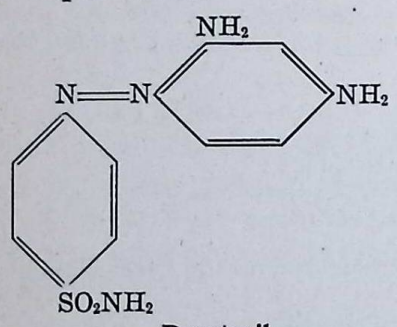
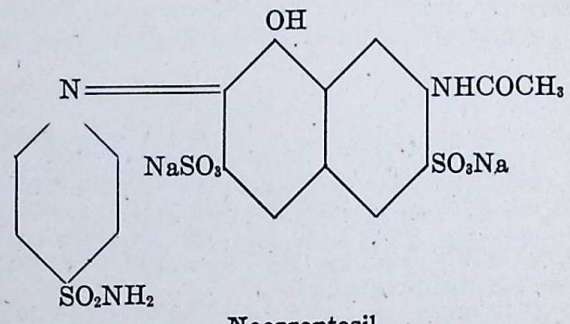
berger and Jacobs, in 1919, had noted the bactericidal effect of compounds of the sulfanilamide type; but they had failed to pursue their observations. In 1932 Mietsch and Klarer synthesized sulfamidochrysoidin or **prontosil** as it was designated, which Domagk in the same year demonstrated could protect mice infected with beta hemolytic streptococci. His results, however, were not published until 1935 after preliminary clinical reports had appeared on the use of the drug in human streptococcic infections. In 1935, another soluble compound designated as **neoprontosil** was introduced by the same investigators. Prontosil (4-sulfonamido-2,4-diamino-azobenzene) is sulfanilamide in an azo (N=N) linkage with diaminobenzene; neoprontosil is the analogous compound formed with the 7-acetylamino-1-oxy-3,6-sodium disulfonate of naphthalene.



Prontosil



Neoprontosil

Soon after the introduction of prontosil, the Tréfouels, Nitti and Bovet, showed that this compound was decomposed in the body and that its simpler component, para-aminobenzene sulfonamide (sulfanilamide), actually exerted all of the effects previously attributed to the more complex prontosil. This finding was soon confirmed in other laboratories and with the application of sulfanilamide in the treatment of human infections, its effectiveness, particularly in streptococcal infections, was soon amply demonstrated.

Despite its remarkable therapeutic action in streptococcal infections, sulfanilamide was found to be relatively inactive in other common bacterial infections and in addition proved rather toxic, inducing acidosis and a bluish discoloration of the blood when administered over a long period. An attempt was therefore made to prepare related compounds which proved superior to sulfanilamide in that they were more effective in other than streptococcal infections. In general, polycyclic molecules are less toxic than those containing a single benzene ring and hence various compounds were linked to sulfanilamide to form more complex molecules. Sulfapyridine, in which sulfanilamide is combined with pyridine, was found to be highly effective in infections with the pneumococcus in which sulfanilamide has but feeble action. However, this compound was highly toxic and was soon superseded by sulfathiazole in which the sulfanilamide radical was attached to the thiazole ring instead of to pyridine as in sulfapyridine. This compound not only possessed advantages over sulfapyridine in its lesser toxicity but was also found to be more polyvalent in its antibacterial activity, being effective against a number of bacterial agents—the streptococcus, pneumococcus,

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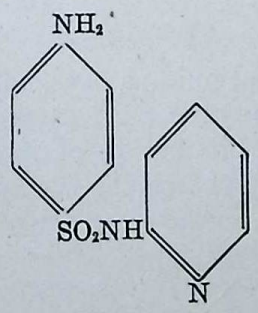
staphylococcus, B. coli, gonococcus, meningococcus, etc. Sulfadiazine, the next important compound to be introduced was superior to its predecessors in its relatively low toxicity and in addition had a rather wide range of activity against bacterial infection so that it in turn became the drug of choice surpassing previously introduced compounds.

A total of several thousand derivatives of sulfanilamide have been prepared but only a few of these have been found to possess sufficient advantages to render them of therapeutic value. In addition to the compounds already mentioned, others have been found of value and are discussed below.

Sulfanilamide, the parent compound of this series of drugs is the amide of sulfanilic acid. It diffuses throughout the body tissues and fluids. When given orally it is absorbed within four to six hours and requires forty-eight to seventy-two hours to be entirely eliminated from the body. Like the other sulfonamide derivatives, it is partially converted to the acetyl derivative in the body and excreted in part in this form. The degree of this acetylation varies in different animals; in man, it is acetylated only relatively slightly (10 to 20 per cent). It induces the toxic reactions common to all the sulfa drugs, except for renal injury secondary to the deposition of the drug in the kidney. It is particularly prone to cause nausea and vomiting. It and sulfacetamide are the two drugs of this series which tend to cause acidosis with a fall in the carbon-dioxide combining power of the blood.

For most purposes sulfanilamide has been displaced by the equally effective and less toxic drugs available and except for several conditions in which it is preferred it is used in cases where other drugs have failed or where, as in acute nephritis, there is danger of renal injury.

Sulfapyridine, the sulfanilyl derivative of pyridine, is much less soluble than sulfanilamide, and is absorbed very irregularly from the gastro-intestinal tract and hence must be administered parenterally when it is desired to maintain adequate and constant blood levels. It



Sulfapyridine

is much more effective against the pneumococcus and was used originally in pneumococcal pneumonias. However, it has given place to the less toxic sulfathiazole and sulfadiazine and is rarely used at present.

Sulfathiazole, the first of the heterocyclic compounds to be introduced into therapy, contains a thiazole ring substituted in the sulfonamide side-chain of sulfanilamide. Although only slightly soluble it is absorbed and excreted rapidly. All of the drug is excreted from the body within

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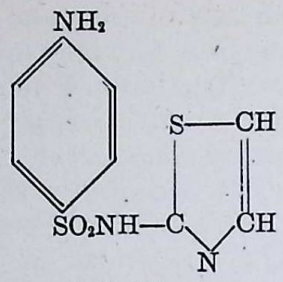
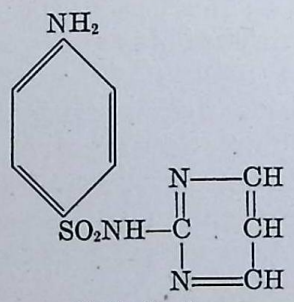
twenty-four hours after the administration of a single dose. About 12 per cent of the injected drug is acetylated in the body but this acetyl



Sulfathiazole

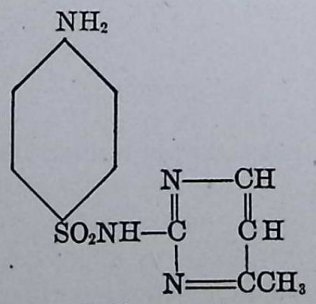
derivative is very insoluble and tends to give insoluble renal concretions. It is more polyvalent in its effects than other sulfonamide derivatives, being effective against the staphylococcus as well as the hemolytic streptococcus, meningococcus, gonococcus and pneumococcus. Although diffusing only poorly into the cerebrospinal fluid of the normal animal this apparently is not the case in infections of the meninges for it has been used successfully in meningitis by oral administration alone.

Sulfadiazine consists of a pyrimidine nucleus attached to sulfanilamide. Administered orally, it is absorbed less rapidly and less completely than sulfathiazole or sulfanilamide and it is conjugated to the acetylated form in a lesser degree than these drugs. It also fails to diffuse into the body fluids as readily as sulfanilamide or sulfathiazole. However, it



Sulfadiazine

passes into the cerebrospinal fluid as does sulfanilamide. It is secreted more slowly than any of the preceding drugs and is only slightly acetylated. It has the unique distinction of forming a relatively soluble acetyl derivative. Its general toxicity is also relatively low so that it has to a large extent displaced the older drugs for general use.



Sulfamerazine

Sulfamerazine, the methyl derivative of sulfadiazine, differs from sulfadiazine chemically in having a methyl group substituted for one of

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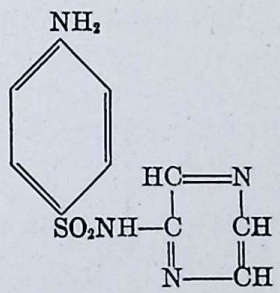
the hydrogens in the pyrimidine nucleus. Unlike certain other methyl derivatives the toxicity of sulfamerazine is not increased over sulfadiazine. The therapeutic action of sulfamerazine is very similar to that of sulfadiazine but it has the advantage over the latter that it can be prepared more easily and is more rapidly absorbed and less rapidly excreted. Hence effective blood levels are attained more rapidly following the oral administration of sulfamerazine than is the case after the administration of equal amounts of sulfadiazine or sulfathiazole. The slower excretion of sulfamerazine also results in the maintenance of the blood level for a longer period and necessitates less frequent administration of the drug to maintain a relatively constant blood level.

The therapeutic indications for the use of sulfamerazine are essentially those of sulfadiazine. The same general toxic manifestations are observed in the case of both drugs, but the incidence of renal involvement is perhaps somewhat less in the case of sulfamerazine.



Sulfapyrazine.

Sulfapyrazine is the sulfanilamido derivative of pyrazine, an isomer of pyrimidine. It differs from sulfadiazine in the relative positions of the N-atoms of the pyrazine ring. Sulfapyrazine resembles sulfadiazine in its low order of toxicity and general actions. It is absorbed and excreted rather slowly and is acetylated only to a small degree. It is secreted into the cerebrospinal fluid reaching concentrations of one-half to two-thirds of the blood level within twelve hours following its intravenous administration.

The indications for the use of sulfapyrazine are similar to those of sulfadiazine. The former drug is claimed to be effective in certain cases of dysentery due to strains of shigella resistant to other sulfonamides.

Intestinal Antiseptics.—Several sulfonamide derivatives have been prepared for use as intestinal antiseptics. These compounds are absorbed only poorly from the gastro-intestinal tract and hence permit the attainment of a high concentration of the drug in the lumen of the gut where they exert their action.

Sulfaguanidine (sulfanilylguanidine), a combination of sulfanilamide and guanidine, was the first of the intestinal antiseptics of the sulfonamide series to be introduced into medicine. Although fairly soluble in water it is poorly absorbed from the intestinal tract. It has been used for the treatment of bacillary dysentery and in conjunction with surgery on the bowel but has been largely superseded in medical practice by the corresponding sulfathiazole derivatives in surgery and by the use of

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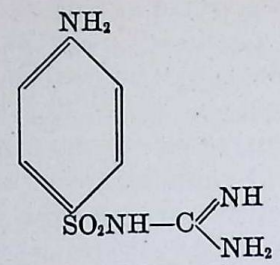
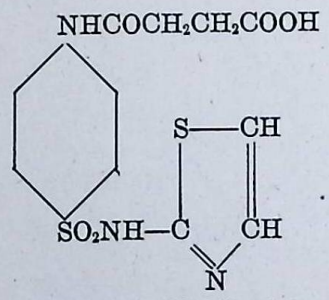
systemic anti-infectives such as sulfathiazole or sulfadiazine in the treatment of bacillary intestinal infections.



Sulfanilylguanidine

Succinylsulfathiazole (Sulfasuxidine), a combination of sulfathiazole and succinic acid, is only slightly absorbed from the gut. The drug is inactive *in vitro* and probably owes its action in the intestine to the liberation of sulfathiazole. It reduces markedly the bacterial flora as

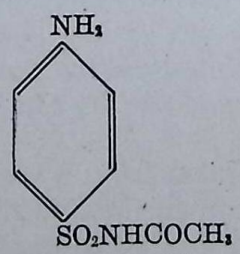


Succinylsulfathiazole

demonstrated by the reduction in the count of the coliform organisms in the stool which is rendered semifluid and practically odorless after adequate therapy.

Phthalylsulfathiazole [2-(N^4-phthalyl-sulfanilamide) thiazole], a condensation product of phthalic anhydride and sulfathiazole, is the most recent of the intestinal antiseptics introduced into medicine. It differs from sulfasuxidine in containing phthalic acid instead of succinic acid linked to sulfathiazole. It is only very slightly absorbed from the gut and is superior to sulfasuxidine in that much smaller doses are required to elicit the same therapeutic response.

Sulfacetimide (N^1-acetyl-sulfanilamide) commercially designated as sulamyd or albucid was introduced for use as a urinary antiseptic. It



Sulfacetimide

contains an acetyl group in the —SO_2NH_2 side-chain of sulfanilamide rather than in the —NH_2 group, the position acetylated when sulfanilamide is administered.

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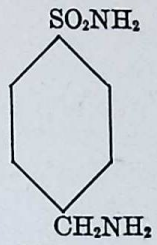
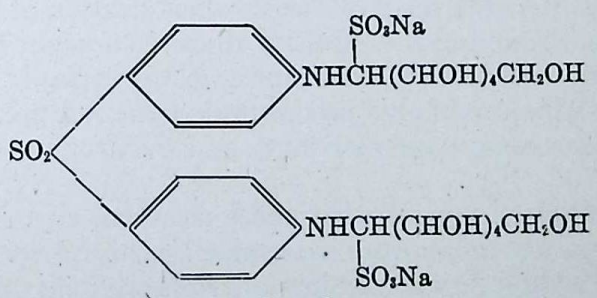
Sulfamylon (marfanil, sulfabenzamine, homosulfanilamide, mesudin) is of interest in the fact that unlike the other sulfonamide derivatives the amino group is separated from the benzene ring by a methylene group. It is a *p*-aminomethyl benzene sulfonamide instead of *p*-aminobenzene sulfonamide as in the case of sulfanilamide. Like the other sulfonamides



Sulfamylon

it is active against gram-positive organisms such as pneumococci, streptococci, staphylococci, etc., but is also effective against some gram-negative bacteria and anerobic as well as aerobic organisms. Its principle interest lies in the fact that it is apparently superior to the other sulfonamide drugs when applied locally.

Promin, a diamino-diphenylsulfone derivative of glucose has attracted interest because of its effectiveness against the tubercle bacillus in the



Promin

experimental animal. Unfortunately its toxicity precludes its usefulness in the human. It has also been used in the treatment of leprosy.

Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) is better tolerated, is non-toxic in animals and is equally as effective as promin. The most recent of this series of compounds is **promizole**, (4-aminophenyl-2¹-aminothiazoyl-5¹-sulfone) which is well tolerated by humans and is under clinical trial. It is claimed to have been curative in a case of tuberculous meningitis, usually a uniformly and rapidly fatal disorder. Most recently the antibiotics (particularly streptomycin) combined with one of the above-mentioned drugs have been used experimentally in the treatment of tuberculosis.

Other Sulfonamide Derivatives.—A number of other sulfonamide derivatives have been introduced into medicine but have not been widely used. Some, like globucid, disulon, uliron and irgamid have been used abroad. **Globucid** is the ethyl derivative of sulfathiazole. The methyl derivative of sulfathiazole is toxic being particularly apt to cause neuritis.

N^4-sulfanilyl-sulfanilamide (**disulon** or diseptal C) and its mono-

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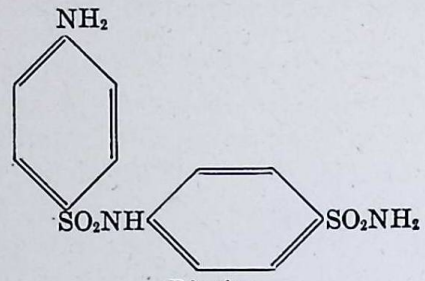
methyl derivative **(diseptal B)** have also been used therapeutically. The dimethyl derivative, diseptal A or **uliron**, has been most widely employed. The methyl group in these compounds is substituted for the hydrogen of the SO_2NH_2 group.



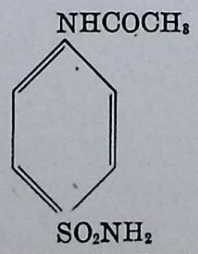
Disulon

Action.—The experimental evaluation of a sulfonamide drug involves the determination of its acute and chronic toxicity in the normal experimental animal, its effects on various organisms *in vitro*, its activity in the infected animal, the study of its absorption, excretion and distribution in the organism, and the changes undergone by the drug in passing through the host as well as its clinical evaluation in human infections.

The concentration of the sulfonamides in the blood, urine or tissues may be determined with relative ease by diazotization of the drug with nitrous acid and coupling the resulting diazo compound to form a dye the concentration of which is determined colorimetrically (Bratton and Marshall). By the use of this procedure it has been possible to study the absorption, excretion and distribution of the drug in the tissues and body fluids.

The physical, physiological, pharmacological and chemical properties of the various sulfonamide drugs determine their behavior in the organism. Thus their solubility determines their absorbability and suitability as intestinal antiseptics. Their rate of absorption and excretion determines the dosage and frequency of administration, as well as their potential usefulness as urinary antiseptics. Those drugs which are highly concentrated in the urine may serve as urinary antiseptics. However, the insolubility of most of the effective compounds causes their precipitation in the urinary tract and thus limits their use for this purpose.

Most of the sulfonamides are **acetylated** in the body. This acetylated form is usually inactive therapeutically and in some cases less soluble than the parent substance. This results in their precipitation in the tissues and is probably partly responsible for some of the toxicity shown



Acetylsulfanilamide

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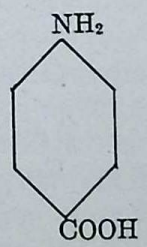
by the drugs. In the process of acetylation, an acetyl group is introduced into the amino group attached to the benzene ring. Only in such compounds in which this group already contains a substituent does acetylation fail to occur.

The primary action of the sulfonamide derivatives is bacteriostatic, these drugs inhibiting the multiplication of the invading organisms and allowing the normal cellular defensive mechanisms of the body to suppress the infection. The drugs do not act on the normal defense mechanisms of the organism, neither the production of antibodies nor the normal phagocytic activity being affected by the drugs. Unless these normal mechanisms are capable of response, the drugs fail to eradicate an infection. In general, there is a fairly good correlation between the *in vitro* activity of a given sulfonamide and its *in vivo* action. However, no simple procedure is available for the determination *in vitro* of the probable effectiveness of a given drug.

Although the sulfonamides in general are bacteriostatic they may exert a bactericidal effect when present in high concentrations under certain conditions. Thus in certain urinary infections, the high concentrations of the drug may actually sterilize the urine when the pH of this fluid is optimal.

The exact **mechanism** whereby the sulfonamide derivatives as well as the antibiotics and antiseptics generally exert their action is still unknown. All of these agents act by killing or inhibiting the growth of the infectious agent in the invaded tissues of the host rather than by stimulating defense mechanisms of the body, by decreasing the toxic manifestations, or by otherwise rendering the organism resistant to the invading pathogens and their toxins.

It is very probable that the bactericidal and bacteriostatic action of the antiseptic drugs depends upon the reaction of the drug with some chemically reactive group of the cell. These receptors, as they were designated by Ehrlich, are probably of diverse type. In some cases, the drug attaches itself to the surface layer of the invading organism thereby interfering with its normal activities. In other instances the drug unites with some vital enzyme system of the bacteria. Such enzyme systems may either be inactivated by their union with the drug or because of the similarity in molecular structure of the drug and normal substrate, the former reacts with the enzyme, thereby blocking reactions requisite for the multiplication of the bacteria.



Para-aminobenzoic acid

In the case of the sulfonamide derivatives, the available evidence indicates that they exert their antibacterial effects by competition with

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certain substrates as just outlined. This view is based on the observation of the existence of certain antagonists to the sulfonamide drugs. The principal antagonist is para-aminobenzoic acid which plays a rôle in the metabolism of many bacteria and which resembles sulfanilamide in its chemical structure. Because of this resemblance, it is assumed that the enzyme system of the bacteria combines with the sulfonamide instead of with their normal essential constituent, para-aminobenzoic acid, and that further metabolic activities upon which multiplication depends, remains in abeyance.

The above described theory accounts for the ineffectiveness of the sulfonamide drugs in the presence of pus or products of tissue destruction. The latter contain ample amounts of para-aminobenzoic acid which competes with the available drug.

Although suggestive of the general type of mechanism involved, it is unlikely that the simple theory of competition with para-aminobenzoic acid completely accounts for the action of the sulfonamide drugs. For example, the chemical constitution of marfanil as well as some of the more complex sulfonamide drugs differs from that of para-aminobenzoic acid to such a degree as to render the hypothesis outlined improbable. It can only be said that it is probable that these drugs react so as to interfere with some phase of bacterial metabolism vital to their continued multiplication.

Toxicity.—The sulfonamide drugs, in general, are remarkably inert insofar as their physiological effects and acute toxic effects in the experimental animal are concerned. In mice, for example, the peroral **L. D. 50** (the minimal lethal dose that will kill 50 per cent of the animals) of sulfanilamide is between 3 and 4 grams per kilogram of body weight and the growth rates of young rats are not appreciably disturbed by the daily administration of from 0.25 to 1 gram per kilogram of body weight The drug thus possesses a relatively low degree of toxicity which is even less pronounced in some of the other members of this group. However, the toxic effects noted in man frequently represent idiosyncrasies to the drug that are not reproducible in animals and it is these manifestations which are of importance in their practical use.

The toxic reactions observed following the use of the various sulfonamide derivatives vary to some extent with the different members of this group. Sulfanilamide and sulfapyridine are prone to give violent reactions; sulfathiazole is less toxic; while sulfadiazine, sulfamerazine and the drugs used as intestinal antiseptics are least apt to give undesirable reactions.

In sensitive individuals the administration of even a half gram or less of the drug may result within an hour or two in a rise in body temperature, headache, nausea and other evidences of acute toxicity. Rarely reactions suggestive of anaphylaxis may occur (Black-Schaffer).

Anorexia, Nausea and Vomiting are common complications which follow the use of the sulfonamides. It is least frequent, occurring only in about 5 per cent of patients, receiving sulfadiazine or sulfamerazine. It is not uncommon, as already indicated, following the administration of sulfathiazole and sulfanilamide and almost always occurs after sulfa-

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pyridine. These toxic reactions are probably secondary to effects of the drug on the central nervous system. Other evidences of such **central action** are headache, dizziness and lassitude. These may suggest alcoholic intoxication and from the frequent occurrence of these symptoms the driving of an automobile or other pursuits in which dizziness may lead to accident should be forbidden in the course of sulfanilamide therapy. Although **neuritis** is a rare complication following the commonly used sulfonamides, its occurrence has prevented the adoption of some derivatives which otherwise showed promise of therapeutic usefulness.

Dermatitis consisting of a morbilliform rash sometimes follows the use of the sulfonamide compounds. It usually appears several days to a week after beginning the administration of the drug and when accompanied by fever may be mistaken for one of the exanthematous diseases. In rare cases the continuation of the drug may lead to exfoliative dermatitis.

Toxic manifestations resulting from untoward effects of the sulfonamide drugs on the hematopoietic system are among the more serious complications of this form of therapy. An acute or slowly developing **hemolytic anemia** may be encountered usually in patients who have received the drugs for two or more weeks, but may also occur at an earlier time. **Leukopenia** and **granulocytopenia** may occur abruptly at any time but most often also after prolonged courses of therapy. Because of these changes in the blood, frequent blood counts are essential with prompt cessation of therapy when complications appear.

Among the other alterations in the blood seen during sulfonamide therapy are **thrombocytopenia** which occurs occasionally and may be sufficiently severe to give rise to purpura.

Sulfanilamide also causes a bluish discoloration of the blood which is evidenced by **cyanosis** and has been attributed to the formation of methemoglobin as well as to the formation of some unidentified oxidation product of this drug.

Acidosis, with a lowered carbon dioxide combining power of the blood, occurs commonly after the ingestion of sulfanilamide. The only other drug of the series tending to give this reaction is sulfacetamide but in the doses with which this is usually used, this is of little practical significance.

One of the most serious toxic effects of the sulfonamide drugs, with the exception of sulfanilamide, is their effect on the **kidney**. Since the commonly used drugs as well as their acetyl derivatives are relatively insoluble in water and since the drugs are concentrated in the urine, it is apparent that there will be a tendency for them to precipitate in the urinary tract. This is particularly true of sulfathiazole and sulfapyridine but may also occur with sulfadiazine. The precipitation of concretions of these drugs may lead to complete occlusion of the urinary tubules.

The urinary complications which follow the administration of sulfanilamide derivatives will be determined by the solubility of the various drugs and their N^4-acetyl derivatives in the urine and the concentration of the drug in the urine which is determined by its rate of excretion.

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Acetylsulfathiazole is the least soluble of the group in urine whereas sulfathiazole is the most soluble in acid urine. Since sulfathiazole is excreted rapidly it is evident that levels which exceed the solubility particularly of the acetylated derivative may easily be attained and lead to renal complications when this drug is used.

The **solubility** of certain of the sulfanilamide derivatives in urine is markedly increased by an increase in alkalinity. This, however, is not universally true, the solubility of acetylsulfathiazole, acetylsulfapyridine and sulfapyridine, being little affected by a change in pH from 5.5 to 7.5. On the other hand, the solubilities of sulfathiazole, sulfadiazine, sulfamerazine, acetylsulfadiazine and acetylsulfamerazine are 2½, 8, 4, 8 and 5 times, respectively, as soluble at pH 7.5 as they are at 6.5. It is obviously desirable to maintain the urine in an alkaline state during the administration of these drugs so as to help avoid their deposition in the urinary tract. This may be done by the concurrent administration of bicarbonate of soda or other alkalinizing salts. In addition, it is imperative that the urinary volume be maintained above 1,500 cc. to avoid undue concentration of the drugs which would favor their deposition. This is particularly true during warm weather or in patients in whom the urinary output may be diminished. Daily examination of the urine for red blood cells should also be made for evidence of early renal damage and attention given to pain in the flank as a sign of kidney involvement.

With alkalinization and the maintenance of an adequate urinary volume, renal complications are infrequent. However, the urine should be examined at intervals for the appearance of red blood cells and pain in the inguinal region noted, as these are usually the first evidence of renal irritation.

Sulfanilamide has not been demonstrated to cause renal complications. Hence, it is preferred in cases in which there is preëxisting renal damage (*e. g.*, acute nephritis).

A rare renal complication of sulfonamide therapy is **cortical necrosis** (or toxic nephrosis) of the kidney.

Certain of the toxic reactions such as nausea and vomiting, are more common following the use of certain of the drugs (sulfanilamide, sulfapyridine) than others and hence may at times be avoided by changing to another member of the series. However, a patient showing reactions attributable to an **idiosyncrasy** to the drugs will usually manifest this to all members of the series and is liable to have a more severe reaction if one or another of these compounds is prescribed a second time. Hence, great care must be taken when these drugs are given to patients who previously have had a reaction. Repeated administration of the sulfonamides apparently leads to **sensitization** similar to that seen with other allergens.

In vast scale experiments in which sulfadiazine has been used prophylactically in the armed forces, the incidence of mild toxic manifestations has been reported to be about ½ per cent with severe reactions in only one individual in 10,000. However, when larger doses of this drug or sulfamerazine are used in the treatment of infections the incidence of

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toxic manifestations is much greater as shown in the accompanying table.

INCIDENCE OF TOXIC EFFECTS IN 316 PATIENTS TREATED WITH SULFADIAZINE AND SULFAMERAZINE. (From the Data of Hall and Spink and Clark, Flippin and Murphy.)

Toxic Manifestation		Incidence per cent
Hematuria	Microscopic	5.0
	Gross	0.9
Nausea and Vomiting		4.1
Drug fever		2.5
Dermatitis		2.5
Leukopenia		1.6

Therapeutic Use.—In the therapeutic use of the sulfonamide derivatives, certain general principles should be kept in mind. An exact bacteriological diagnosis is necessary in order to limit the use of the drugs to those conditions in which they are effectual. The empirical use of the drugs is both irrational and dangerous. Only in severely ill individuals, and in epidemics where there is presumptive evidence favoring the diagnosis, is it justifiable to proceed with therapy prior to making an exact diagnosis to determine if sulfonamide therapy is indicated. The promiscuous use of the drugs in minor conditions for which other less toxic substances are available is also to be deprecated.

It is important to maintain a sufficient concentration of the drug in the body in order to elicit its maximal effectiveness and to avoid an excess of the drug which might lead to toxic reactions. Moreover, since a variable proportion of the drug is converted to the acetyl derivative which is inactive therapeutically, but which nevertheless may exert the toxic effects of the drug, it is desirable to know the concentration of both the free and combined drug present in the blood. Only by frequent blood analyses can optimal blood levels be maintained and toxic levels avoided during the course of therapy.

The particular sulfanilamide derivative to be used in any given clinical condition varies depending upon the nature of the infectious process. Although there is, in general, a marked similarity in their action, certain of the drugs are more effective than others in a given condition. In general, sulfadiazine and sulfamerazine are used where possible because of their relative lack of toxicity and untoward reactions which follow their use. They are used particularly in infections due to meningococci, pneumococci, staphylococci, streptococci, or Friedländer's bacillus. Sulfadiazine is considered to be the drug of choice in infections due to Lancefield's Group A organisms. These drugs are also used in undulant fever although their effectiveness in this disease is questionable. Sulfathiazole is more polyvalent in its action. It is considered the drug of choice in infections due to *E. coli*, trachoma, gonococcal infections, pneumonia due to staphylococci, staphylococcic infections generally, and in tularemia. However, recent evidence would indicate that sulfadiazine is as effective as sulfathiazole in the treatment of staphylococcic infections. Sulfathiazole is also used in genito-urinary tract infections. These are usually of a mixed type and the drug appears in higher concentrations

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in the urine. Acetylsulfanilamide is also used in urinary tract infections, due to its being relatively non-toxic in the small doses necessary for maintaining an effective concentration in the urine. Sulfanilamide is the drug of choice in actinomycosis, chancroid, lymphogranuloma venereum, in acute nephritis and in erysipelas.

There is usually definite evidence of therapeutic effectiveness within twenty-four to forty-eight hours following the administration of a sulfonamide drug if this has been administered in ample dosage in a susceptible infection (*cf.* Fig. 73). Should the desirable response not be evident after a suitable period of trial, another member of the sulfonamide series should be substituted or preferably an antibiotic be used if the organism is susceptible to the latter. In the case of the sulfonamides, sulfathiazole and sulfapyridine are the drugs of second choice in infections due to pneumococci, meningococci or in tularemia. Sulfanilamide is the second choice in trachoma and in infections due to streptococci and *B. coli.*

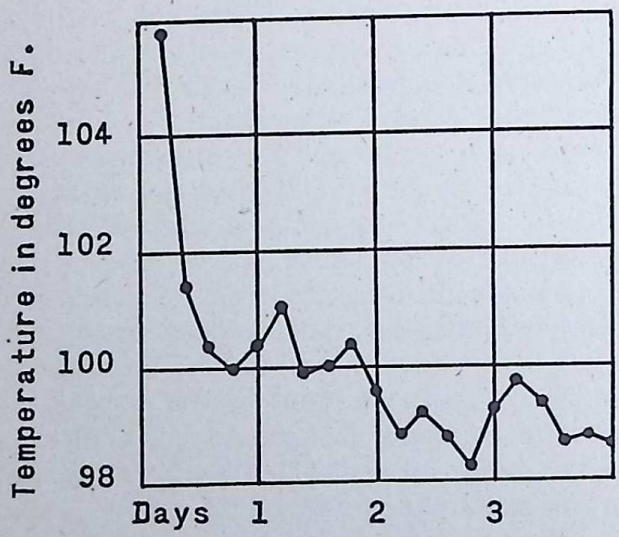

FIG. 73.—The effect of sulfadiazine in meningococcus meningitis. Chart showing the rapid decline in the body temperature of a patient ill with meningococcus meningitis, following the administration of sulfadiazine. Within forty-eight hours of the patient's entry into the hospital and the beginning of therapy the body temperature had declined to normal.

None of the sulfonamides are active against the enterococcus group of streptococci or the anerobic streptococcus infections. They are also ineffective in rheumatoid arthritis.

Although clinical data would indicate the effectiveness of the sulfonamides in the treatment of infections due to hemolytic streptococci Groups B and C, in the *Clostridia, Hemophilus influenzæ* and in brucellosis and tularemia, the evidence is not convincing. The newer antibiotics show promise of being the drugs of choice in these infections.

With the increasing use of **penicillin,** this drug is now used in many of the conditions previously treated with the sulfonamides. The introduction of the newer preparations of penicillin for oral administration renders this drug convenient (although expensive) even in the

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treatment of the less severe infections in which the sulfonamides have heretofore been preferred.

The infections in which penicillin is ineffective and in which the sulfonamides are indicated are the group of gram-negative bacillary infections including colon bacillus infections, the bacillary dysenteries, infection with the Friedländer bacillus and soft chancre. Some of these are best treated with streptomycin when this is available.

In the treatment of pneumococcal pneumonia, sulfadiazine is highly effective although identical results are now obtained by the use of penicillin which is now preferred due to its lower toxicity. There is some evidence to indicate that a synergism exists between the sulfonamides and penicillin so that the use of both drugs may ultimately be desirable in certain severe infections.

In **urinary tract infections**, the use of the sulfonamides has in many cases proved effective. Certain pathogens of the urinary tract, particularly the *streptococcus fecalis*, are resistant to these drugs and hence a bacteriological diagnosis prior to therapy is desirable. Infections with *streptococcus fecalis* and *B. coli* are at present best treated with mandelic acid.

Attempts have been made to obtain derivatives of the sulfonamide drugs which would not be absorbed from the gut and exert an **antiseptic** action on the bacteria of the **intestinal contents.** The problem faces several inherent difficulties. Any highly insoluble drug would fail to intermingle with the intestinal contents and would in any case probably be inert. A slightly soluble compound, on the other hand, would inevitably be absorbed to some extent because of the ready permeability of the intestinal wall. A second difficulty in effecting intestinal antisepsis results from the fact that the pathogens are present in the crypts and sometimes even in the walls of the intestine which would necessitate the use of a systemic drug for their eradication. Most of the pathogens of the intestinal tract are gram-negative organisms which are resistant to the action of the sulfonamides. Nevertheless, a certain amount of success has been obtained by the use of the sulfonamides in intestinal infections either by systemic administration of sulfadiazine or sulfathiazole or by the use of the relatively insoluble derivatives—sulfaguanidine, sulfasuxidine or sulfathalidine. These have been used principally in the treatment of bacillary dysentery, and in surgery involving the large bowel. Administration of sulfasuxidine or sulfathalidine prior to operation results in a greatly reduced count of the bacterial flora of the intestinal contents and lowers the incidence of morbidity following surgery on the colon. Their postoperative use in these cases also reduces the postoperative sequelæ and shortens the period of convalescence (Poth).

In enteric disorders of short duration, for example in *Shigella paradysentery*, the administration of succinylsulfathiazole does not ameliorate the illness nor shorten its duration (Roberts and Daniels). However, the carrier rate may be reduced by the use of the drug in this condition. In the bacterial dysenteries most practitioners prefer the use of the

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systemic drugs—sulfadiazine or sulfathiazole—to the insoluble intestinal antiseptics.

Local Use.—Following their introduction, the various sulfonamide preparations were often applied locally to wounds, burns, into infected cavities, on the peritoneum, etc. This was done as a prophylactic measure to avert subsequent, as well as to eradicate existent, infection. In the presence of pus or necrotic tissue, as we have seen, the sulfonamides have little or no effectiveness. Moreover, their repeated use for minor infections tends to induce sensitivity to the drugs and there is always the danger of toxic reactions. For these reasons and because of the availability of the effective antibiotics, the local use of the sulfonamides has gradually fallen into disrepute and their use is only rarely advocated for this purpose.

In the local application of the sulfonamides it is necessary to keep in mind that these drugs are readily absorbed from denuded areas or mucous membranes. When applied in excessive amounts (over 10 to 15 grams) the usual toxic effects due to overdosage may be induced and hence quantities in excess of 10 grams should not be used. In applying sulfonamide preparations locally, the usual surgical procedures such as débridement should also be utilized. In burns a solution of sulfadiazine has been used. This is sprayed at regular intervals over the burned areas for three or four days until a thin eschar is formed. Blood levels of the drug should be determined at frequent intervals, as considerable amounts may be absorbed when the drug is applied in this way.

Prophylaxis.—During the course of the early years of the Second World War the sulfonamides were used rather widely for the prophylaxis of threatened systemic infections as well as for local application to wounds. The reported results indicated that sulfadiazine administered routinely to a large group of individuals controlled outbreaks of scarlet fever, streptococcus infections of the throat and meningococcic meningitis. The administration of 2 grams of sulfadiazine daily for two days has been shown to be effective against carriers of the meningococcus thereby averting threatened epidemics of meningococcal infection. The routine administration of sulfathiazole prior and subsequent to exposure to gonorrheal infection appeared to reduce markedly the incidence of this disease.

The sulfonamides have also been used prophylactically in the treatment of children who have suffered an attack of rheumatic fever. Individuals who have had one attack are subject to subsequent attacks of this disease which is now looked upon as being in the nature of a tissue reaction to a streptococcic infection. By preventing upper respiratory infections it was hoped that subsequent attacks of rheumatic fever might be avoided. The preliminary results with this form of therapy appear promising. It should be emphasized, however, that the use of the sulfonamides in the acute or active phase of rheumatic fever is dangerous.

Dosage.—The dosage of the various sulfonamides commonly employed is determined by the blood level of the free drug which it is desired to maintain. This, in turn, will vary to some extent in different

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individuals and will be determined by the completeness of absorption, the rapidity with which the drug is excreted in the urine and the degree with which the drug is acetylated. In ordinary infections it is desired to maintain a blood concentration of 8 to 10 mg. per 100 cc. of sulfanilamide and 5 to 10 mg. of sulfapyridine, sulfathiazole, sulfadiazine or sulfamerazine, in ordinary infections and 10 to 15 mg. per 100 cc. in the case of critically ill patients. The average dose necessary to accomplish this is 0.1 gram per kilogram of body weight as the initial dose in the case of sulfanilamide with subsequent doses of one-sixth of this amount every four hours. For sulfapyridine, sulfathiazole and sulfadiazine, the dose is 4 grams initially followed by 1 gram every four hours. Sulfamerazine is administered in doses of 3 grams initially and 1 gram every six hours thereafter. The above doses are altered when necessary to maintain the desired blood level. Therapy should be continued throughout the night in order to avoid a decrease in blood level during this period. To maintain an alkaline urine 2.6 grams (40 gr.) of sodium bicarbonate are administered concurrently with each dose of the sulfonamide.

Where the prompt attainment of a therapeutic blood level is not feasible by oral administration, as, for example, in seriously ill patients, or those who are vomiting or are unconscious, parenteral therapy is indicated. For this purpose the sodium salts of the drugs are used. For intravenous administration, the dose of the sodium salts of sulfapyridine, sulfathiazole, sulfadiazine, or sulfamerazine is 0.06 gram per kilogram of body weight with one-sixth of this amount after six hours for each milligram per cent rise in blood concentration desired. These are given in 5 per cent aqueous solution. Sulfanilamide, when administered parenterally, is given by hypodermoclysis in a 1 per cent solution in normal saline or sixth-molar sodium lactate solution.

As already indicated, successful therapy requires prompt therapy, the maintenance of an effective blood level, and the avoidance of toxic effects due to overdosage. This can only be accomplished by frequent determination of the blood levels of the drug.

The intestinal antiseptics are administered in high dosage. Sulfaguanidine when used in the treatment of bacillary dysentery is given in doses of 0.05 gram per kilogram of body weight followed by a maintenance dose of a similar amount every four hours, day and night.

Sulfasuxidine is administered in doses of 0.25 gram per kilogram of body weight followed by one-sixth of this amount every four hours.

In the local application of the sulfonamides to open wounds or burns, approximately 0.1 gram sterilized drug is distributed per square inch with a maximum of 10 grams used over any twenty-four hour period.

In prophylaxis a dosage of 1 to 2 grams of the drugs per day suffices.

The use of an adequate dosage of the sulfonamides is not only necessary for effective therapy but failure to do this may lead to drug fastness on the part of the infecting organism. It is also important to maintain the patient on the drug for a sufficient period after the disappearance of fever. Thus in pneumococcic pneumonia, therapy should be continued until the temperature has been normal for seventy-two hours; in the case of severe streptococcic, staphylococcic and meningococcic infections, for

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five to seven days. In the latter conditions the drug may even be continued in smaller doses after this time until the complete recovery of the patient is assured.

PREPARATIONS

U. S. P.

SULFANILAMIDUM, sulfanilamide, a white crystalline powder, very slightly soluble in water. Dose, 2 grams.

TABELLÆ SULFANILAMIDI, sulfanilamide tablets. Dose, 2 grams.

SULFAPYRIDINUM, sulfapyridine, a white or faintly yellowish crystalline powder, practically insoluble in water. Dose, 2 grams.

TABELLÆ SULFAPYRIDINI, sulfapyridine tablets. Dose, 2 grams.

SULFAPYRIDINUM SODICUM STERILE, a sterile aqueous solution of the sodium salt of sulfapyridine for intravenous injection. Dose, 2 grams.

SULFATHIAZOLUM, sulfathiazole, a white or faintly yellowish crystalline powder, practically insoluble in water. Dose, 2 grams.

TABELLÆ SULFATHIAZOLI, sulfathiazole tablets. Dose, 2 grams.

SULFATHIAZOLUM SODICUM, sulfathiazole sodium, a white to faintly yellowish white powder, soluble in water. Dose, 2 grams.

SULFATHIAZOLUM SODICUM STERILE, a sterile aqueous solution of sodium sulfathiazole for intravenous injection. Dose, 2 grams.

SULFADIAZINUM, sulfadiazine, a white or slightly yellow powder, practically insoluble in water. Dose, 2 grams.

TABELLÆ SULFADIAZINI, sulfadiazine tablets. Dose, 2 grams.

SULFADIAZINUM SODICUM, sulfadiazine sodium, a white powder, soluble in water. Dose, 2 grams.

SULFADIAZINUM SODICUM STERILE, a sterile aqueous solution of sodium sulfadiazine for intravenous injection. Dose, 2 grams.

SULFAGUANIDINUM, sulfaguanidine, a white crystalline powder, practically insoluble in water. Dose, 2 grams.

TABELLÆ SULFAGUANIDINI, sulfaguanidine tablets. Dose, 2 grams.

SUCCINYLSULFATHIAZOLUM, succinylsulfathiazole, a white powder, practically insoluble in water. Dose, 2 grams.

TABELLÆ SUCCINYLSULFATHIAZOLI, succinylsulfathiazole tablets. Dose, 2 grams.

B. P.

SULPHANILAMIDUM. Dose, 0.5 to 1 gram.
TABELLÆ SULPHANILAMIDI. Dose, 0.5 to 1 gram.
SULPHAPYRIDINA. Dose, 0.5 to 2 grams.
SULPHAPYRIDINA SOLUBILIS. Dose, 0.5 to 2 grams.
TABELLÆ SULPHAPYRIDINÆ. Dose, 0.5 to 2 grams.
SULPHATHIAZOLUM. Dose, 0.5 to 2 grams.
SULPHATHIAZOLUM SOLUBILE. Dose, 0.5 to 2 grams.
TABELLÆ SULPHATHIAZOLI. Dose, 0.5 to 2 grams.
SULPHADIAZINA. Dose, 0.5 to 2 grams.
SULPHADIAZINA SOLUBILIS. Dose, 0.5 to 2 grams.
TABELLÆ SULPHADIAZINÆ. Dose, 0.5 to 2 grams.
SULPHACETAMIDUM. Dose, 0.5 to 2 grams.
SULPHACETAMIDUM SOLUBILE. Dose, 0.5 to 2 grams.
SULPHAGUANIDINA. Dose, 0.5 to 2 grams.
TABELLÆ SULPHAGUANIDINÆ. Dose, 0.5 to 2 grams.

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U. PENICILLIN AND OTHER ANTIBIOTICS

I. PENICILLIN

The discovery of penicillin and its introduction into medicine has been called rightfully "the greatest contribution of medical science of the twentieth century." Its discovery not only made available what is undoubtedly the most potent chemotherapeutic agent known, but opened an entirely new field of therapy—the use of substances derived from moulds, bacteria, and other lower organisms which have been designated as antibiotics.

Historical.—In 1929, Alexander Fleming while examining culture plates of staphylococci noted that the organisms surrounding a growth of mould, which had accidentally contaminated the culture plate, had undergone lysis. He proceeded to culture the mould and demonstrated that the nutrient broth in which it had grown acquired the inhibitory bactericidal properties which had been noticed in the original culture plate. The mould responsible for the production of this hitherto unknown bactericidal substance was subsequently demonstrated to be a strain of *Penicillium notatum* and the term **penicillin** was therefore used by Fleming to designate the active bactericidal substance elaborated by this fungus. Fleming also showed that the bactericidal activity of

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penicillin was specific for certain organisms and that on injection in animals, preparations of broth containing penicillin activity were relatively non-toxic. Since penicillin was ineffective against the *Hæmophilus influenzæ* of Pfeiffer, it was first used to inhibit contaminants in the isolation of this bacillus. However, in view of its non-toxic and non-irritant character, Fleming, as early as 1929, suggested the possibility of utilizing penicillin as an efficient antibacterial agent for injection into areas infected by organisms sensitive to it.

The discovery of Fleming received little attention during the following decade. However, during this period the remarkable success attained with the sulfonamide derivatives as chemotherapeutic agents and the recognition of their deficiencies stimulated interest in penicillin. Chain, Florey, and their associates at Oxford undertook the purification of extracts containing penicillin and demonstrated their remarkable antibacterial properties against a number of organisms including the anerobes. They demonstrated its effectiveness in the experimental animal as well as in a few human patients. The acute need for an effective, non-toxic, antibacterial substance during the war then in progress prompted the inauguration of a program by the United States Governmental authorities which soon led to the production on a large scale of ample supplies of penicillin.

Chemistry.—The first preparations of penicillin used were relatively crude concentrates of the filtrate from the broth on which the mould had grown. The active principle may be extracted by organic solvents (ether, amyl acetate, etc.) from its aqueous solution after acidification. Further purification is carried out by retransferring the active principle to water, adsorbing it on charcoal and eluting. Penicillin is also available in crystalline form. It has the empirical formula $C_{14}H_{19}NO_6$ and is an acid which forms crystalline sodium, calcium and other salts.

Several isomeric forms of penicillin have been identified and designated as penicillin **F**, **G**, **K** and **X** or as I, II, IV and III, respectively. Commercial preparations prepared from deep vat cultures consist for the most part of penicillin G, but those prepared from shallow cultures may contain appreciable amounts of penicillin X. Both forms are therapeutically effective, but their effectiveness against different organisms differs. Thus penicillin X appears to be more effective in the treatment of gonorrhea than is penicillin G, whereas the latter is more effective than the former in the treatment of syphilis. Penicillin K is largely inactivated in the body. Hence the blood levels attained following its administration are low and its therapeutic action is feeble.

The isomeric penicillins in dilute mineral acid are converted to the corresponding penillic acids which are dibasic acids with the structure shown in the accompanying formula. The structure of penicillin itself is represented by the accompanying formula. In this formula, R represents an aliphatic or aromatic radical which is characteristic for each of the known varieties of penicillin. The side chain, RCH_2, in the formula for penicillin is a Δ^2-pentenyl ($CH_3 \cdot CH_2 \cdot CH = CH \cdot CH_2$—) group in penicillin F; a benzyl ($C_6H_5 \cdot CH_2$—) group in penicillin G; a n-heptyl (C_7H_{15}—) group in penicillin K; and a para-hydroxybenzyl ($HO \cdot C_6H_5 \cdot$

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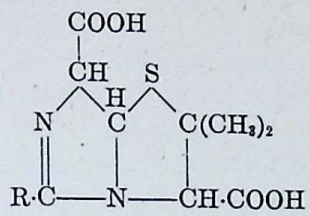
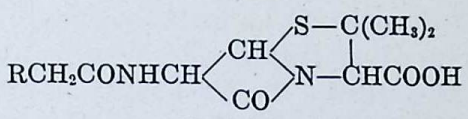
CH_2—) group in penicillin X. It is apparently the $-\underset{\underset{O}{\|}}{C}-N<$ grouping in the penicillin molecule which is essential for its biological activity.



Penill c acids

Although the synthesis of penicillin has been reported, the naturally occurring compounds prepared from moulds remains the source of the penicillin of commerce.



Penicillin

As used therapeutically penicillin is an amorphous, brownish-yellow solid which readily dissolves in water, saline or glucose solution. The sodium salt of penicillin is hygroscopic and deliquesces in contact with the air. Because of this property, the calcium salt is sometimes preferred.

Esters of penicillin have been prepared. These are ineffective and toxic when administered parenterally but are more effective than the salts of penicillin when administered orally.

Standardization.—The potency of penicillin is at present expressed in terms of international units arrived at by a collaborative assay of a single lot of penicillin by a number of laboratories. The international unit is essentially equal to the Oxford unit which was the amount of penicillin activity which formed a zone of inhibition 24 mm. in diameter around a cylinder in an agar plate inoculated with *Staphylococcus aureus*. One milligram of the crystalline sodium salt of penicillin contains 1,667 international units. Thus 20,000 units, the average dose, corresponds to approximately 12 mg. of pure penicillin.

Mode of Action.—The mechanism of action of penicillin is not known. This drug apparently may act either as a bacteriostatic or as a bactericidal agent depending on the experimental conditions. The antibacterial action is related to the concentration of the drug and is not affected by the presence of pus or products of tissue degeneration. Penicillin differs from the sulfonamide derivatives in its mode of action. Hence organisms resistant to the action of penicillin may be susceptible to the sulfonamides and *vice versa*.

Bacteria may become resistant to penicillin if subjected to sublethal concentrations of the drug. This acquisition of drug fastness is of practical importance since the use of inadequate doses may lead to the development of refractoriness in an infection initially reactive to the drug. To avoid this hazard of the development of fastness to penicillin,

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it is essential that effective doses be intensively applied at the very beginning of a course of treatment.

In general, the antibacterial activity of penicillin, like that of other chemotherapeutic agents, is highly selective. It is chiefly effective against aerobic or anaerobic, gram-positive organisms, although not all gram-positive organisms are susceptible to its action. However, the same organism may manifest a great difference in the susceptibility of various strains. Thus despite the general susceptibility of staphylococci, some strains are highly resistant to penicillin, and this variability is particularly striking among the Streptococci viridans. This variation in the sensitivity of strains is of great practical importance in determining the dosage to be administered in a given case.

Most gram-negative organisms are resistant to penicillin. Thus it is ineffective against the colon-typhoid group which includes *E. coli*, *B. typhosus*, and the Salmonella. It is also ineffective against many other common organisms listed in the accompanying table. The resistance of certain bacteria to penicillin is probably due to their capacity to elaborate inhibitors which are capable of inactivating the drug. Thus suspensions of *E. coli* contain an intracellular enzyme, "penicillinase," which inhibits penicillin.

In addition to its action in bacterial diseases, penicillin is also effective in diseases due to certain spirochetal agents, moulds (actinomycosis), and virus disorders (ornithosis). Its effectiveness in syphilis appears now to be well established.

Antibacterial Activity of Penicillin

Susceptible Species	Insusceptible Species
Pneumococcus	H. influenzæ
Streptococcus	E. coli
Staphylococcus	B. typhosus
Meningococcus	Salmonella
Gonococcus	Proteus
Treponema pallidum	Pyocyaneus
Diphtheria	Friedländer's bacillus
Anthrax	Monilia
Tetanus	Tuberculosis
Actinomyces	Shigella
Cl. welchii	Blastomyces
B. subtilis	Streptocoecus fecalis
V. septique	B. Prodigiosus

Absorption and Excretion.—Injection of penicillin intravenously results in an initially high concentration of the drug in the blood with an abrupt fall with only traces remaining after one-half to three hours depending on the dose injected.

After an intramuscular injection of 40,000 units the blood level rises to a maximum within ten minutes and is maintained for almost two hours after which it gradually decreases. Absorption following subcutaneous injection is slow. When administered by rectum, penicillin is for the most part destroyed by the intestinal bacteria. Penicillin is rapidly absorbed following its instillation into the duodenum. It is only slowly absorbed following injection into body cavities. It also

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diffuses very slowly in the normal from the blood into the spinal fluid and *vice versa*.

Penicillin is eliminated in the urine from which over half of the amount injected may be recovered. In the presence of renal insufficiency the drug is retained and the blood level remains high. The excretion of penicillin by the kidney apparently occurs as a result of tubular excretion. Following the injection of para-aminohippuric acid the rate of excretion of penicillin is reduced, both drugs competing for the same portion of the nephron. The administration of 2 grams of benzoic acid every three hours has also been claimed to be an effective means of blocking the excretion of penicillin and of thus maintaining higher and sustained blood levels.

Toxicity.—Penicillin is practically non-toxic and rarely are untoward reactions observed following its therapeutic use. It is this relative absence of undesirable effects which has led to its displacement of the sulfonamide drugs in the treatment of many infections.

Urticarial reactions occasionally follow the use of penicillin and may occur even after its local application. Thrombophlebitis is not infrequently observed following the intravenous injection of the drug which should always be well diluted and injected slowly when this route of administration is used. Chills and fever were formerly also observed but with greater purity of the marketed preparations and the elimination of pyrogenic agents, this reaction has become rare. Patients may also complain of some discomfort at the site of an intramuscular injection. This may be counteracted by the addition of a local anesthetic, but this is rarely necessary. Penicillin is not a potent antigen, for even after the administration of huge doses of the drug over long periods of time, as in the treatment of subacute bacterial endocarditis, positive skin reactions to the intradermal injection of the drug are not seen.

Apparently some of the reactions observed following the use of penicillin are due to impurities which comprise a considerable portion of the material as ordinarily marketed. However, sensitization to the drug itself may also occur but this is relatively uncommon.

Therapeutic Use.—Penicillin has displaced the sulfonamide derivatives in the treatment of a variety of infections due to susceptible organisms. It is used in all **staphylococcic infections** such as acute or chronic osteomyelitis, carbuncles, meningitis, sinus thrombosis, pneumonia, empyema, etc. The drug is superior to any available chemotherapeutic agents in the eradication of staphylococcic infections.

Penicillin is also used in all hemolytic **streptococcic infections** with bacteremia and in all serious local infections such as cellulitis, mastoiditis, puerperal sepsis, peritonitis, etc. Similarly it is the drug of choice in infections due to clostridia, anaerobic streptococci, pneumococci, gonococci, anthrax, and Vincent's infection. It is used in all cases of sulfonamide-resistant pneumococcic pneumonia, or meningococcic infections.

Penicillin has been used with success in the treatment of certain cases of **bacterial endocarditis.** When this is due to susceptible organisms as is often the case, long-continued treatment (three weeks or more) has

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eradicated the infection in this previously almost universally fatal disease. It is necessary in treating this condition to determine *in vitro* the susceptibility of the infecting organism to the drug for in many cases massive doses (100,000 units or more every three hours) may be necessary to overcome the infection. Similarly, large doses are also advocated in **peritonitis.**

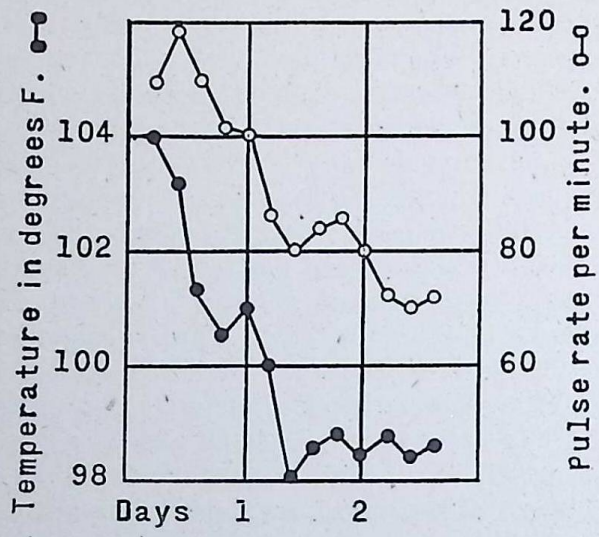

FIG. 74.—The effect of penicillin in pneumococcal pneumonia. Chart showing the rapid decline in the body temperature and pulse rate of a patient suffering from lobar pneumonia following the administration of 20,000 units of penicillin intramuscularly at four hour intervals. Within thirty-six hours of the patient's entry into the hospital and the beginning of therapy the fever and tachycardia had disappeared.

The pneumococcus is one of the most susceptible of the pathogenic organisms to penicillin (*cf.* Fig. 74) which inhibits the growth of the bacillus *in vitro* with as little as 0.01 to 0.02 units per cubic centimeter. The striking achievements of chemotherapy in the treatment of the **pneumonias** is shown by the reduction in the mortality rate of lobar pneumonia from 28 per cent during World War I to approximately 0.7 per cent during World War II. The response in pneumococcic pneumonia treated with sulfadiazine and with penicillin are almost identical except for a more abrupt fall in temperature and fewer instances of extension to another lobe during therapy with penicillin (Kinsman, *et al.*). The injection of 10,000 units four times daily for three days sufficed to produce clinical cures but smaller doses are accompanied by relapses and failures to respond to treatment. Primary atypical pneumonia is unaltered by treatment with penicillin.

In **gonorrhea** and its complications, penicillin is the drug of choice. Only in rare cases are resistant organisms encountered as is the case when the sulfonamide drugs are used. In most cases complete eradication of the disease may be effected in the course of twenty-four to forty-eight hours. By the use of slowly absorbed preparations of penicillin in beeswax, a single injection may in many cases suffice. Since penicillin is rapidly excreted by the kidney it is also effective in infections of this

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organ by susceptible organisms, *e. g.* in carbuncle of the kidney. On the other hand, the common infections of the urinary tract by gram-negative bacteria do not respond to penicillin therapy. In mixed infections of the bladder and urinary tract, penicillin appears in the urine in a concentration which suffices to eradicate the gram-positive and other susceptible organisms.

Penicillin is also of value in gas gangrene and malignant edema due to clostridia infections. However, the usual surgical procedures and antitoxin must also be employed in conjunction with chemotherapy. Favorable results are also obtained following the use of penicillin in the treatment of anthrax.

One of the most notable advances in the treatment of **syphilis** has been the demonstration of the effectiveness of penicillin in this disease. It is of interest that the *Treponema pallidum*, the spirochete of syphilis, is relatively resistant to penicillin when tested *in vitro*. According to the data available at present it would appear that penicillin is the most effective and satisfactory method of treating pre-natal syphilis. In early syphilis (first and second stages) the administration of penicillin in doses of 40,000 units every three hours for seven and one-half days (giving a total of 2.4 million units) is the treatment of choice. The percentage of apparent cures following this form of therapy may be further increased by the simultaneous injection of bismuth salicylate every other day for ten days with the additional administration of 40 mg. of mapharsen daily for eight consecutive days. In neurosyphilis, the use of penicillin with half the usual course of fever therapy is advocated. In cardiovascular syphilis, the use of penicillin is contraindicated, for in this condition a Herxheimer reaction (with fatal outcome) may ensue.

Among the other spirochetes which are susceptible to penicillin are Vincent's organism and Spirillium minus (or Streptobacillus moniliformis), the cause of rat bite fever. The clinical value of penicillin in relapsing fever, Weils' disease (leptospirosis icterohemorrhagica), and other spirochetal disorders is still under investigation.

Because of the susceptibility of Corynebacterium diphtheriæ to penicillin *in vitro*, this drug has been used in the treatment of diphtheria in combination with antitoxin. Its value in this disease is questionable since animals infected with the organism are not protected against the disease.

Among the virus and rickettsial infections which preliminary studies in animals indicate may be susceptible to penicillin are ornithosis and psittacosis which are caused by a virus and murine typhus caused by a rickettsial agent. The clinical value of the drug in similar diseases in man has not been established.

Dosage and Mode of Administration.—Penicillin may be administered by a variety of routes depending upon the nature of the condition which is being treated. For intravenous and intramuscular administration the sodium or calcium salts of penicillin are used. These are available in the form of a golden-yellow, amorphous solid which may be dissolved in sterile water, isotonic saline or 5 per cent glucose for injection. In

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order to delay its absorption and thus avoid the necessity of repeated injections penicillin is also available in the form of a suspension of the calcium salt in a menstruum of white wax dispersed in peanut oil. This is injected intramuscularly. Penicillin is also available commercially in the form of a crystalline sodium salt containing 95 per cent of penicillin G. This preparation has the advantage over the amorphous preparations in that it is stable at room temperature, and may be administered subcutaneously with virtually no local reaction.

The dosage of penicillin and its optimal mode of administration will vary with the severity and nature of the condition under treatment. For serious illnesses, intravenous or intramuscular injection is indicated. If injected directly through a syringe, penicillin is administered in a concentration of 10,000 to 50,000 units per cc. For constant intravenous therapy a more dilute solution containing 25 to 50 units per cc. of saline or 5 per cent glucose is used. For intramuscular injection the more concentrated solution containing 10,000 to 50,000 units per cc. is used so as to lessen the total volume of fluid injected. This is the route of choice since intravenous injection may lead to thrombosis of the veins and subcutaneous injections are painful.

In serious infections an initial dose of 15,000 or 20,000 units is followed by a constant intravenous injection at the rate of 5,000 to 10,000 units per hour or 20,000 to 40,000 units injected intramuscularly every two to four hours. In general, effective blood levels vary from 0.02 to 0.16 units per cc. However, in certain serious infections as much as 100,000 units may have to be injected every two to three hours.

In the treatment of gonorrhea, 25,000 units are injected intramuscularly every three hours for five doses with repetition of the course of therapy where necessary. This necessitates continuous treatment (day and night). However, it is probable that with the newer slowly absorbed preparations (for example the peanut oil—beeswax suspensions), a single injection may suffice for adequate treatment.

Penicillin may also be injected directly into body cavities, for example into the pleural cavity or into a joint or abscess cavity. These cavities should be aspirated prior to the injection of the penicillin. The injection of 120,000 units into a pleural cavity after the aspiration of an effusion will ensure a bacteriostatic concentration of the drug in the blood stream for twenty-four hours.

Since penicillin does not penetrate the subarachnoid space in appreciable amounts, it is injected intracisternally or into the subarachnoid space in the treatment of meningitis.

In bacterial endocarditis penicillin is administered for three weeks or more by the intramuscular injection of 200,000 to 300,000 units daily in divided doses at two to four hour intervals.

Penicillin in oil and wax is injected intramuscularly as a single injection or at eight to twelve hour intervals in doses of 100,000 to 300,000 units.

For oral therapy buffered penicillin is administered in doses of 20,000 to 50,000 units every two or three hours. This should be administered on a fasting stomach not less than thirty minutes before or not less than one and one-half hours after meals.

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For topical application ointments containing 250 units per gram are used for application to the eye, or to superficial infections of the skin.

Troches containing 500 units of penicillin may be allowed to dissolve in the mouth two or three times a day for the treatment of Vincent's infection.

Oral Penicillin.—Although the earlier studies indicated that most of the penicillin administered orally was destroyed by the acidity of the normal stomach, it was subsequently shown that doses of 90,000 units given by mouth, one-half hour before breakfast gave serum levels comparable to those obtained from 15,000 to 20,000 units given intramuscularly. In achlorhydric individuals, higher serum levels were sustained even when penicillin was taken orally before a meal. The fact that penicillin was also effective when introduced into the duodenum also suggested that it was the gastric acidity which caused its destruction following oral administration.

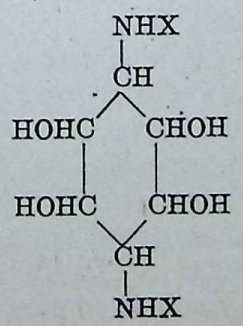
In order to overcome the destructive effects of gastric acidity on penicillin and thus permit its administration orally, several procedures have been devised. The drug may be buffered or buffer salts such as aluminum hydroxide, aluminum dihydroxyaminoacetate, sodium citrate, calcium or magnesium oxide, etc., may be administered with it. It may also be administered in hardened gelatin capsules which are impervious to the gastric contents. A suspension of the drug in oil has also been found suitable for oral administration as have also certain esters of penicillin.

In conditions in which small doses of parenteral penicillin are effective, oral administration is feasible. However, in severe infections requiring treatment in large doses, parenteral administration should be used to initiate therapy.

For topical application penicillin is marketed in several forms: (1) as an ointment for local application, (2) as a fine powder for installation into a cavity, (3) in the form of troches for use in infections of the mouth and throat and (4) as dental cones for insertion into the socket following extraction of a tooth.

II. STREPTOMYCIN

Next to penicillin, the most important of the antibiotics which has thus far been investigated is streptomycin, discovered by Waksman in *Actinomyces griseus*.



Streptamine and streptidine

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Chemistry.—Streptomycin is easily converted to two degradation products, streptamine and streptidine, the structures of which are probably represented by the accompanying formula in which X = H in streptamine and X = $-C\begin{matrix}\diagup\!\!\!\diagup NH \\ \diagdown NH_2\end{matrix}$ in streptidine (Carter *et al.*). The chemical structure of streptomycin itself is as yet unknown. Its empirical formula is $C_{21}H_{39}N_7O_{12}$ and it contains three basic functional groups—streptidine, N-methyl glucosamine, and a six-carbon, nitrogen free hexose. The disaccharide formed by the union of the last two mentioned compounds has been designated as streptobiosamine.

Absorption and Excretion.—Streptomycin like penicillin is rapidly absorbed following its parenteral administration and excreted in the urine. It is also concentrated in the bile. When administered orally, little of the drug is absorbed. Since it is neither absorbed nor destroyed in the gastro-intestinal tract, the oral administration of the drug is limited to conditions in which a reduction in the number of susceptible bacteria present in the bowel is desirable.

Assay.—An S unit of streptomycin has been defined as the amount of material which will inhibit the growth of a standard strain of *E. coli* in 1 cc. of medium. An L unit equals 1,000 S units. One gram of streptomycin base is equivalent to 1,000,000 S units and a microgram of the base equals 1 unit. Following repeated injections of 100,000 units, blood levels of 12 to 25 units per cc. are attainable.

Toxicity.—Parenteral administration of streptomycin to susceptible laboratory animals often produces fatty changes in the kidneys and liver. Such toxic effects have not been demonstrated in the human. However, undesirable reactions are not uncommon. These consist of flushing of the face, headache and a fall in blood pressure, resembling the effects of histamine intoxication. These toxic effects are presumably due to impurities present in the available preparations. Following long-continued administration of the drug, damage to the vestibular portion of the eighth cranial nerve has been reported. This reaction is usually compensated for after several weeks.

Therapeutic Use.—Because of the greater difficulty attending its manufacture commercially, streptomycin has been available only in limited quantities. However, it gives promise of being effective against many organisms which are resistant to the action of both penicillin and the sulfonamides.

Streptomycin like penicillin, is of very low toxicity and may also be administered parenterally. It is effective against both gram-positive and gram-negative bacteria and gives promise of being of value in the treatment of such infections as typhoid fever, the bacillary dysenteries, *E. coli* infections, etc. Streptomycin is also effective against the tubercle bacillus *in vitro* and protects guinea-pigs against infection with this organism. However, its value in the human has not as yet been demonstrated although it may perhaps ultimately find a place in the treatment of this disease. The drug in preliminary studies also appears to be effective in the treatment of tularemia, influenzal meningitis, brucel-

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losis, and infections due to Aërobacter aërogenes, Pseudomonas aëruginosa, Salmonella, etc.

Streptomycin is administered by the intermittent intramuscular, subcutaneous, intravenous, or intrathecal routes. It may also be administered by nebulization in infections involving the respiratory tract. The total daily dose which has been used varies from 1 to 2 million S units (Herrell and Nichols). This is administered in single intramuscular injections of 1 or 2 cc. containing 125,000 units per cc.

Many strains of bacteria rapidly develop a resistance to streptomycin. When used therapeutically, therefore, adequate dosages must be used over a sufficiently long period of time to avoid the development of drug-resistant strains.

Streptothricin is derived from *Actinomyces lavendulæ* and like streptomycin is effective against both gram-negative and gram-positive bacteria. Despite a relatively low acute toxicity, it shows cumulative toxic effects and hence gives less promise of value compared to streptomycin

Other antidiotics derived from Actinomycetes are **Actinomycin A** prepared from *Actinomyces antibioticus*, and **Proactinomycin**, prepared from *Proactinomyces gardneri*, but both of these are very toxic.

III. TYROTHRICIN AND OTHER BACTERIAL ANTIBIOTICS

Among the antibiotics derived from bacteria, are **tyrothricin** which is a mixture of **gramicidin** and **tyrocidine.** These were isolated by Dubos from the soil bacillus (*Bacillus brevis*). Gramicidin and tyrocidine have been isolated in crystalline form. Both are fairly active against certain gram-positive cocci but when injected in relatively small doses they induce hemolysis and death. Because of their high toxicity the clinical use of these antibiotics has been limited to tyrothricin.

More recently **Gramicidin S** has also been obtained from *Bacillus brevis* and offers promise of usefulness for the local therapy of gram-positive and gram-negative infections.

Other antibiotics derived from bacteria are **pyocyanase** and **pyocyanin** (from *Pseudomonas aëruginosa*), which have been known for many years but which are inactive *in vivo*, and **subtilin** and **bacitracin** (from *B. subtilis*) which are effective against gram-positive bacteria.

Of the above-mentioned compounds, only tyrothricin has been used in medical practice. It is available in the form of a concentrate in an isotonic solution containing 0.5 mg. of tyrothricin per cc. It is applied locally by instillation, irrigation or wet dressing. It may be instilled into body cavities such as the para-nasal sinuses, urinary bladder or pleural cavity but may not be used for parenteral injection because of its toxicity.

IV. OTHER ANTIBIOTICS DERIVED FROM BACTERIA AND MOULDS

The success of penicillin has led to an investigation of other antibiotics. The various fungi, bacteria, and other microscopic forms of life are potential sources of antibiotics. In their struggle for existence, these organisms have developed constituents which protect them against

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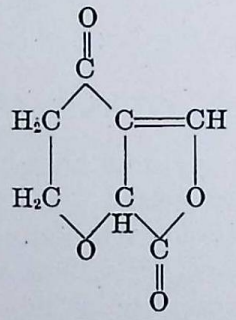
other microbial agents. The soil particularly is rich in such organisms and has been most widely investigated. In addition to penicillin and streptomycin, a number of such agents have been described and in some cases isolated. Their sphere of usefulness has, however, not been as wide as that of the substances already described and hence they need only be considered briefly.

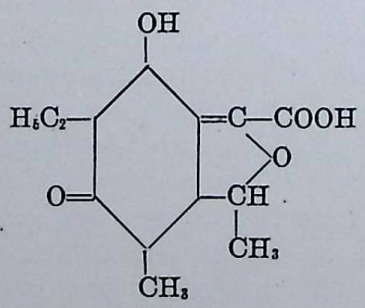
Clavacin has been isolated from *Aspergillus clavatus* (Waksman, Horning and Semner). This antibiotic is bactericidal in high dilutions against gram-negative microörganisms, and bacteriostatic for certain common fungi. It is highly toxic on intravenous or intramuscular injection. Although it has not undergone clinical trial as yet, clavacin promises to have usefulness against such local or superficial fungus diseases as Monilia albicans (thrush), Oidium asteroides (Blastomyces dermatitis), and Trichophyton gypseum (epidermophytosis).

Patulin, derived from *Penicillium patulum* is identical to clavacin. It has been shown to be a relatively simple compound with the structure shown in the accompanying formula.



Patulin

Aspergillic acid is derived from Aspergillus flavus. It is active against gram-positive bacteria and against the tubercle bacillus *in vitro*. The toxicity of the available preparations is apparently due to impurities and not to the pure compound itself. This has prevented their use in therapeutics except for local application.



Citrinin

The chemical structure of aspergillic acid is shown in the accompanying formula.

A number of other antibiotics derived from moulds have been described in recent years but have not attained any therapeutic importance. Among these may be mentioned penatin, notatin and penicillin B which apparently are different names for the same chemical substance, citrinin,

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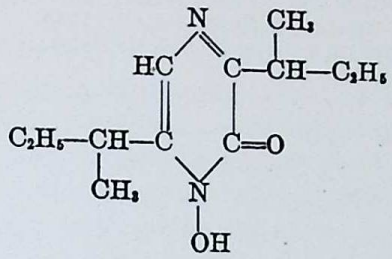
citricin, gliotoxin, fumigatin, chætomin and others. Of these, the structure of citrinin has been determined. As noted in the accompanying formula, it is a relatively simple compound as are indeed others of this group of drugs. This gives hope to the view that further study will result in the synthesis of new compounds of therapeutic significance.



Aspergillic acid

Antibacterial substances have also been derived from other than microbial sources. Among these may be mentioned **lysozome**, discovered by Fleming in 1922 in nasal secretions, and which is, therefore, of historical interest inasmuch as it was the first antibacterial agent to attract the attention of the discoverer of penicillin. Chlorellin, obtained from an algæ (Chlorella vulgaris), canavalin, from soy beans, allicin from garlic, and other substances having a limited antibacterial action have also been described, but none of these has attained a rôle of any importance in therapeutics.

Although only a few of the many antibiotics thus far discovered have proven of practical therapeutic value, the widespread distribution of these substances in nature has opened a wide field for investigation. Further work may uncover agents which will complement the action of penicillin and aid in the eradication of infections not remediable by the antibiotics available at present.

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PART IV

Anthelmintics

ANTHELMINTICS are drugs which are used to kill or remove intestinal worms. They are often divided into vermicides and vermifuges, according as they kill or merely cause the expulsion of the worm, but this is determined largely by the quantity which comes in contact with the parasite and the rapidity with which the bowel is evacuated.

In order to possess any value as an anthelmintic, a drug must, of course, act more strongly on the parasite than on the host, and this more intense effect may be attained either by a specific action on the parasite, or by the drug failing to be absorbed from the alimentary canal. As a matter of fact, the anthelmintics, with few exceptions, have not been shown to possess any such specific action, but seem to injure most forms of living matter; this has been demonstrated more particularly for muscle tissue. Their use is thus rendered possible only by their slow absorption which permits of their acting on the parasite in greater concentration than on any of the tissues of the host.

COMMON HELMINTHIC DISEASES AND DRUGS USED IN THEIR TREATMENT

Disease	*Common designation*	*Helminth*	*Drugs used in therapy*
Trichuriasis (trichocephaliasis)	Whipworm or threadworm	Trichuris trichiura	Leche de higueron (ficin) Santonin Hexylresorcinol Tetrachlorethylene Oil of chenopodium
Enterobiasis (oxyuriasis)	Pinworm or seatworm	Enterobius vermicularis	Gentian violet Hexylresorcinol Phenothiazine
Ascariasis	Large roundworm	Ascaris lumbricoides	Hexylresorcinol
Uncinariasis (ancylostomiasis)	Old world hookworm	Ancylostoma duodenale	Tetrachloroethylene
Necatoriasis	New world hookworm	Necator americanus	Tetrachloroethylene
Strongyloidiasis	Strongyloidosis	Strongyloides stercoralis	Gentian violet
Diphyllobothriasis	Broad or fish tapeworm	Diphyllobothrium latum	Oleoresin of aspidium (male fern)
Tæniasis solium	Pork tapeworm	Tænia solium	Oleoresin of aspidium
Tæniasis saginata	Beef tapeworm	Tænia saginata	Oleoresin of aspidium
Hymenolepiasis nana	Dwarf tapeworm	Hymenolepis nana	Hexylresorcinol

Before the administration of most of the anthelmintics, the bowel ought to be emptied of its contents as far as possible by a light, easily digested diet and a laxative; and a brisk purge ought to follow some hours later, in order to remove the dead or stupefied worms. The anthelmintic is often prescribed along with a purge.

A number of parasitic worms infest the human giving rise to varied and often severe disorders. These helminthic diseases are of particular importance in tropical medicine. In the accompanying table are listed

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the commoner parasitic worms encountered and the chief drugs used in their treatment. The table includes the Nematodes, round or threadworms, and the Cestodes or tapeworms. A third important group of helminthic diseases are caused by the Trematodes, which include the Schistosomiases and other flukes. The latter are considered elsewhere (p. 163).

The earliest anthelmintics used were derived from plant products—santonin, chenopodium, aspidium, pelletierine, etc. These have been largely replaced by less toxic and more effective chemicals such as tetrachlorethylene, hexylresorcinol, gentian violet, etc., which have replaced the toxic chemicals such as thymol, or naphthol, formerly used.

I. MALE FERN (ASPIDIUM FILIX-MAS)

A number of ferns contain bodies which present considerable resemblance to each other from a chemical as well as from a pharmacological point of view, and which may therefore be classed together, at any rate until further information is available regarding them. The best known of these is the male fern (Aspidium filix-mas), obtained by extracting the green rhizomes and stipes of Dryopteris filix-mas.

The active constituents of this remedy are *Filicic Acid* and other related neutral and acid bodies: *Aspidinin*, *Flavaspidic Acid*, *Albaspidinin*, *Aspidinol*, *Filmaron*, and *Flavaspidinin*. These bodies are all derivatives of phloroglucin and butyric acid, and it is still uncertain whether the effects of male fern are to be attributed to any one of them or whether all of them may not share in the action. Jacquet holds that the chief therapeutic factor is the filmaron, but that the others also have some effect.

Nearly related bodies have been found in Aspidium athamanticum (Uncomocomo), which contains two forms of *Pannic Acid*, and in Aspidium spinulosum, while smaller quantities of acids occur in a large number of ferns. Several of these ferns enjoy a reputation as anthelmintics for tapeworm, and their virtues are generally considered due to these bodies.

Cusso (Kousso, Brayera) the pistillate flowers of Brayera anthelmintica and **Kamala** derived from Mallotus Philippinensis contain kosotoxin and rottlerin, respectively, which are also phloroglucinbutyric acid compounds and exert an anthelmintic activity similar to that of male fern.

Action.—The extract or oleoresin of male fern, which is the only one of these plants used in regular medicine, as a general rule passes through the bowel without causing any symptoms whatever. The quantity of active substance dissolved, while sufficient to destroy the parasite, is too small to produce any effects on the host, and escapes with the other contents of the bowel, or if absorbed does not cause any symptoms. In rare cases, however, where large quantities are administered, or where some unknown conditions favor the absorption and retention of an unusually large amount of the active constituents grave and even fatal symptoms may supervene. These consist in vomiting and purging, with acute pain in the abdomen, muscular weakness, confusion and somnolence, with occasional twitching of the muscles, or slight convulsive movements, collapse, coma, and death. The stomach and intestine are found congested and swollen, and some-

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times covered with small ecchymoses. In some cases icterus has been observed to follow the administration of male fern, probably from the duodenal catarrh, but possibly from destruction of the red blood cells, the number of which has been found to be diminished in some instances (Georgiewsky). In other cases permanent or temporary blindness has resulted from neuritis and subsequent atrophy of the optic nerve.

Therapeutic Uses.—Male fern is used exclusively in the treatment of the several varieties of intestinal tapeworm infections. Previous to its administration the bowel ought to be emptied, as far as possible, by a moderately light diet for one or two days and, by a saline purgative on the night preceding treatment. The oleoresin, or liquid extract, is then to be administered in three doses at half-hour intervals, each dose consisting of a capsule containing 20 minims of the drug, and a second saline purgative is given about two hours later. The dose for children is 1 minim for each year of age up to twelve years. In case the parasite fails to be dislodged, several days ought to be allowed to elapse before a second dose is given. Alcohol, fats, and oily substances should be avoided during the "cure," as they dissolve the active bodies, and thus promote their absorption. Marked anemia, general debility and chronic alcoholism seem to predispose to male-fern poisoning, and the drug is accordingly to be used with care in these conditions. Complete bed rest before, during, and after treatment is desirable.

II. PELLETIERINE

The bark of the pomegranate (Punica granatum) contains a very large amount of tannic acid (20 to 25 per cent), along with several alkaloids, of which *Pelletierine* or *Punicine*, and *Isopunicine* alone are active in ordinary doses. All the pomegranate alkaloids are closely related chemically to each other and to tropine (see Atropine). None of them can be classed among the more active poisons as far as man and the higher animals are concerned. Pomegranate has been used as an anthelmintic, but the crude bark has now been displaced almost entirely by pelletierine tannate which consists of a mixture of the several alkaloids.

In man, large doses cause heaviness, confusion, giddiness, and very marked weakness of the limbs. The consciousness is but little affected but the sight is often dim and uncertain, and in one case complete blindness persisted for several days. Occasionally nausea and discomfort in the abdomen are complained of, and more rarely vomiting, tremors, and cramps of the leg muscles are produced; the gastric symptoms are perhaps due to the large quantity of tannic acid in the drug rather than to the alkaloids.

Pelletierine and isopunicine have a specific action on tapeworms, a solution of one part in 10,000 being sufficient to kill them in ten minutes, while a stronger solution had practically no effect upon other intestinal worms (Schroeder). Pelletierine tannate is used in doses of 0.25 gram.

The preliminary treatment is the same as that given under male fern, and a purge ought to be given one to two hours after the vermicide.

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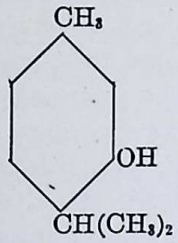
III. THYMOL

Thymol ($C_{10}H_{14}O$) is a crystalline substance obtained from the volatile oil of thyme and other plants, and chemically is a homologue of phenol. It is very insoluble in water and when taken in solid form appears to be absorbed from the alimentary tract with difficulty.



In man, thymol has caused depression, nausea, vomiting, headache and confusion with roaring sounds in the ears and alarming weakness of the heart resulting in giddiness and collapse. In a few cases death has occurred. Its irritant action on the mucous membrane may cause burning sensations in the stomach and vomiting.

In poisoning in animals it induces a condition of weakness and apathy which passes into collapse and death, generally without any convulsions. Fatty degeneration of the liver, congestion or even consolidation of the lungs, and irritation of the intestine are found *postmortem*. One-half or more of the thymol ingested is destroyed in the tissues; the rest is excreted in the urine in combination with sulfuric and glycuronic acids; it is said to have caused renal irritation in some cases, as shown by the appearance of albumin and even of blood in the urine.

Therapeutic Uses.—Thymol was formerly used widely as an anthelmintic in hookworm disease (ancylostomiasis or uncinariasis) but has been replaced by tetrachlorethylene. It is given in capsules or cachets in doses of 1 to 2 grams (15 to 30 gr.) repeated in two hours and followed in six or eight hours by a brisk saline purge. The bowel should be emptied as far as possible by light diet and an aperient before the treatment is begun. Thymol in 1/10 per cent solution is also used as an antiseptic (see p. 785).

IV. CHENOPODIUM

The oil of chenopodium, the so-called "Oil of American Wormseed" is a volatile oil obtained by distillation from Chenopodium ambrosioides anthelminticum, a weed which is found more or less extensively over the entire United States but which is especially abundant in the southeastern section.

The active constituent of the oil is Ascaridol ($C_{10}H_{16}O_2$) which is present in amounts varying from 45 to 70 per cent. It is obtained from the oil by fractional distillation in a partial vacuum. The remainder of the oil is mainly a mixture of terpenes which apparently are devoid of anthelmintic properties. Ascaridol has been shown to be about 30 per cent more toxic than the whole oil. The drug is very active as an anthelmintic against the ascaris and whipworm (Trichuris) infections, but it is, in common with some other anthelmintics, less efficient against oxyuris and other nematodes.

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The drug is toxic and disagreeable symptoms not infrequently follow its administration and a number of deaths have been reported. In many of the cases which terminated fatally there is evidence that there was overdosage. The symptoms most commonly encountered in the use of the drug are nausea and vomiting with pain in the abdomen and some drowsiness, followed at times by ataxia, convulsions and coma. By far the most common of the more serious signs of intoxication from the drug is due to a disturbance of the ear. This may be merely a tinnitus such as is often seen following the use of quinine but it may go on to more or less complete deafness. The deafness is usually temporary, passing off in a few days or weeks but in some cases it has persisted for years. (It is advised that the drug be used with caution in cases of hook-worm infection with long-standing anemia and with signs of cardio-renal disease as in such patients severe untoward reactions are most likely to occur.)

In dogs and cats the oil of chenopodium produces signs of depression of the central nervous system followed by clonic convulsions. In rabbits excitement is not uncommon. Given by mouth to dogs it produces somnolence with incoordination of the muscles of the extremities, coma and paralysis with death in a few hours. In some animals tremors of the muscles appear, passing on to convulsions and opisthotonus. The oil appears to be more toxic for cats than for dogs and rabbits. Given intravenously it causes a fall of blood-pressure which is probably due to an action on the heart. There is also depression of the respiration.

In cats it is slowly absorbed from the stomach but if given in an emulsified condition it is taken up quickly from the duodenum. Given intravenously the odor is detected very soon in the breath, indicating its rapid excretion by the lungs, but it has not been detected in the urine or bile.

Therapeutic Uses.—Oil of chenopodium has been largely replaced in therapeutics by hexylresorcinol and tetrachlorethylene. The adult dose is 2 cc. This dose is divided into two parts and given in hard gelatin capsules two hours apart and the final dose is followed in two hours by a purgative dose of castor oil. Food should not be taken before the anthelmintic is administered as it seems to markedly lessen the efficiency of the treatment.

To children the drug can be given most easily by dropping it on sugar, 1 drop of the oil for each year of the child's age; this dose to be repeated in two hours and followed in three hours by castor oil.

Smillie and Pessoa recommend that Ascaridol itself be substituted for the whole oil as it is a pure substance of definite chemical composition while the oil is a mixture. The main objection to Ascaridol is the high cost. It should be given to adults in a single dose of 1 cc. upon an empty stomach and followed in one-half hour by a purge of magnesium sulfate.

Against ascaris infections the oil may be given in 5 to 10 drop doses three times daily for two days and followed by a brisk purge.

V. SANTONIN

Santonin ($C_{15}H_{18}O_3$) is an anhydride or lactone of santoninic acid, a derivative of naphthalene. It occurs in Artemisia pauciflora along with a nearly related body (artemisin) and a volatile oil (cineol). Santonin

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is very insoluble in water, but is dissolved by alkalies, with which it forms santonates.

Action.—Owing to its insolubility in water, santonin has only a slightly bitter taste in the mouth. It is partially dissolved in the stomach and passes into the bowel, where it effects the removal of some forms of intestinal worms. Under special conditions part of the santonin may be absorbed in the bowel, however, and general poisoning results without the parasites being affected. A certain amount of absorption occurs in every case, as is shown by the disorders of color vision and by the yellow coloration of the urine. At first, objects appear of a bluish color to the patient, but this aberration is of comparatively short duration and may in fact pass unnoticed. It is followed by a much longer period of "yellow sight" or xanthopsia, during which objects that are brightly illuminated seem to have a yellow tinge, blue seems green, and violet is indistinct, although in dimmer lights the violet may still predominate. In severe poisoning the appreciation of the darker colors becomes very imperfect, and violet and even blue may fail to be distinguished from black. In general the violet end of the spectrum is shortened, while the yellow impresses the retina more vividly than normally. In some cases the senses of taste and smell, and more rarely, of hearing, are also deranged. These symptoms all pass off in the course of a few hours, a second stage of "violet sight" occasionally intervening before complete recovery.

The symptoms produced by the absorption of large quantities of santonin are so uniform in man and the other mammals that it is sufficient to enumerate those observed in experiments on the dog. The first distinct effects are generally twitching of the muscles of the head, frequently beginning on one side. These are followed by rolling of the eyes, grinding of the teeth, flexion and extension of the neck and rotation of the head from side to side, later by regular epileptiform convulsions in which the animal is first thrown into opisthotonos and then into clonic spasms of the limbs and trunk. These are interrupted by intervals of repose during which a curious momentary contraction of all the muscles of the body is often noticed. During the convulsive seizures the respiration is irregular and insufficient, and in fatal cases it fails to return after the convulsion passes off, and the animal dies of asphyxia. In man, some confusion, nausea and vomiting occasionally occur after quantities which are too small to produce convulsions, and in several cases aphasia has been observed. In frogs, convulsions are produced by santonin as in mammals, but they are preceded by a prolonged stage of depression, which is entirely absent in the higher animals.

These symptoms manifestly point to changes in the central nervous system. The xanthopsia is generally referred to a specific action on the retina, though some hold that the central apparatus of vision in the brain is the seat of the action. The condition has been ascribed to a preliminary stimulation and subsequent depression of the sense organs for the perception of the violet and eventually of the blue rays of the spectrum, or more precisely to some obstruction to the regeneration of the substance in the retina which normally appreciates violet rays (Filehne). According to Marshall, whatever may be the intimate mode of

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action of santonin in causing color vision, it is fundamentally one affecting violet receptivity and is of the same nature as that occurring after exhaustion of violet vision by violet light. It appears, therefore, to diminish the perceptibility of the most refrangible rays of the spectrum and possibly to a slight extent that of all rays.

The clonic nature of the convulsions at once points to an affection of the brain rather than of the cord, and the epileptiform convulsions are generally regarded as arising from stimulation of the cortex in the higher animals and man, though the basal cerebral ganglia may also be involved; the sudden contractions observed in the intervals of repose are ascribed to stimulation of the gray matter in the region of the pons.

Santonin undergoes some oxidation in the tissues and is excreted in the feces and urine in several forms, two of which have been isolated from the urine of animals by Jaffe and found to be oxysantonins. After medicinal doses santonin is probably excreted almost wholly as a colored substance and chiefly in the urine. After larger doses traces of unchanged santonin have been found in the urine. The colored compound is yellow in acid urine changing to scarlet upon addition of a caustic alkali, but the constitution of the compounds is unknown. The same colored compound is excreted after the administration of a colorless alkaline santoninate so that the organism in forming the colored compound from santonin and from a santoninate reverses the reaction in the two cases. The colored substance has also been found in the sweat after santonin has been given by mouth, in the blood plasma and in the feces after the administration of potassium santoninate. A close relationship has been shown to exist between the presence of this compound in the urine and the occurrence of the xanthopsia, but whether the disturbance of vision is due to the compound is still undecided.

Santonin is universally used as a remedy for the round worm, Ascaris lumbricoides, and most clinicians believe that it has a specific poisonous action on these animals, and that its undoubted effects are due to its killing them. In experiments on the entozoa outside the body, santonin was not found to be very toxic to them, but this appears to have been due to its not having been completely dissolved in the absence of bile, for Sollmann found it fatal to earthworms in low dilution when bile salts were added. Santonin, like other anthelmintics, often causes active movements in the worms before killing them and they are often expelled in this condition, although this movement ceases very soon afterward from the exposure to cold.

Therapeutic Uses.—Santonin was formerly used to remove roundworms (ascaris) and pinworms (enterobius) from the intestine, but has been replaced by less toxic drugs for this purpose. Its principle application is in the treatment of Trichuriasis (whipworm) when the more effective leche de higueron (ficin) is not available. It is much less effective against tapeworm or other intestinal parasites. It may be prescribed as a powder, or lozenge, or in solution in oil in doses of 0.06 gram (1 gr.) for adults and 0.03 gram ($\frac{1}{2}$ gr.) for children every hour for 2 or 3 doses.

A 5 gr. dose is said by Caius and Mhaskar to be the optimum dose for adults and to be safe. They recommend that the dose should be

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taken three hours after a light evening meal and that the purge be given the next morning. For children the dose should not exceed 1 gr. in twenty-four hours. It is often prescribed in a powder or capsule with calomel. Fasting prior to the therapy is undesirable since this increases the absorption of the drug.

Spigelia.—Pink root (Spigelia maritima) was formerly used as a remedy for round worm. Occasional cases of poisoning have been observed, especially in children, the symptoms consisting in flushing and dryness of the skin, often with some edematous swelling of the face, delirium and stupor followed by dimness of sight or temporary blindness. In the dog and cat its injection is followed by vomiting, great weakness and incoördination of the movements, restlessness, rapid dyspneic respiration and finally by stupor, coma, and death from failure of the respiratory center.

The fluid extract is used to remove round worms, which it seems to affect in very much the same way as santonin. It ought to be preceded and followed by a purge.

Arecoline.—The areca nut derived from the palm (Areca catechu) contains arecoline ($C_8H_{13}NO_2$) which resembles pilocarpine in action and is used in veterinary medicine as a remedy in tapeworm.

VI. CARBON TETRACHLORIDE

Following the introduction of chloroform as a general anesthetic in 1847, the closely related carbon tetrachloride was studied also as to its narcotic properties but it proved to be unsatisfactory and it was discarded as a medicinal agent. In 1921 it was recommended by Hall as a highly efficient and apparently safe remedy for the treatment of hookworm infections and since that time it has been used in many thousands of such cases, showing a high degree of effectiveness.

The drug has a mild local irritant action and its use may be followed by eructations and a feeling of warmth in the epigastrium. More rarely nausea and vomiting may follow its administration. Not uncommonly following these symptoms of local irritation there may be evidences of the general action of the drug such as headache which may last for two or three days, dizziness, and not infrequently drowsiness. These symptoms usually pass off in a brief time and are not important. Pain in the back and hematuria have also been described as occurring in man following the use of the drug. The drug, therefore, is not entirely safe and several deaths have already been reported from its use. The principal pathological lesion which has been described is a central necrosis of the liver. Different species of animals appear to vary considerably in their susceptibility to the poison; the dog and probably man are relatively tolerant while the rabbit is more susceptible. Certain factors seem to lessen human resistance among which may be mentioned the use of alcohol, starvation and in general a poorly nourished condition of the individual. A rich carbohydrate diet and the administration of calcium salts appear to lessen the likelihood of poisoning. As the drug has a distinct cathartic action some of it passes out in the feces not having been absorbed at all, this being especially true if the dose administered has been large. Therapeutic doses (3 cc.) are probably largely absorbed from the intestine and excreted by the lungs.

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The toxicity of carbon tetrachloride has been studied by Lamson and his co-workers. They found that it could be administered to dogs in large quantities if it were given upon an empty stomach and that only slight transient symptoms were produced, this lack of toxicity being apparently due to failure of absorption. However, even small doses given in this way have caused definite liver lesions. In rabbits it was much more toxic. Repeated large doses given to dogs by mouth caused chronic poisoning with symptoms of depression, bilirubinemia, bile in the urine and changes in the liver. Administration of substances such as alcohol (97 per cent) and fatty articles of food (cream and olive oil), apparently aid the absorption of the drug and definitely increase its toxicity.

Inhalation of the vapor of carbon tetrachloride is quite toxic to dogs and produces effects similar to those which follow intravenous administration. These symptoms in an unanesthetized dog consist of excitement, muscular hypertonicity, evidences of anxiety and fright followed by anesthesia and sleep from which the animal may recover in a few minutes. Under ether the injection of the drug causes a stoppage of respiration and a marked fall in blood-pressure which is maintained at a low point for some time. The lesion which is found at autopsy is a massive pulmonary edema with focal hemorrhages.

If the drug is injected into the portal vein there is extensive necrosis of the liver and following this the animal shows depression and becomes markedly jaundiced.

Wells has shown that in dogs 3 cc. doses are completely absorbed in from twenty-four to thirty-six hours and that the rate of excretion, which is high at first, drops rapidly until the fifth hour, after which it remains fairly constant. The odor of the drug appears on the breath early and the lungs are apparently the main avenue of excretion. Traces have been found in the urine.

Due to the widespread use of carbon tetrachloride in various industries as a solvent for rubber, paint, grease, etc., and as a cleansing agent in the dry cleaning industry, cases of poisoning are being encountered from time to time. The substance is usually inhaled, due to its presence in the air in the factories, but it is also absorbed through the skin. The early symptoms are those of headache, nausea, loss of appetite, slight anemia and mental confusion. A mild degree of jaundice is not uncommon as are also various visual disturbances. Removal of the individual from the offending fumes is usually sufficient in the early stages of intoxication and adequate ventilation of rooms where the substance is being used should always be provided.

It is believed that a concentration of carbon tetrachloride of 100 parts per 1,000,000 is safe for continuous exposure of workmen during the working day, and that a concentration ten times as great is safe for short periods of say one-half hour. If there is a concentration of 100 parts per 1,000,000 it is noticeable by a faint characteristic odor. If the odor is more than a faint one an increase in ventilation is called for.

Long continued exposure to the fumes of carbon tetrachloride leads apparently to liver changes which may result in hepatic cirrhosis.

Therapeutic Uses.—Carbon tetrachloride, because of its cheapness, has been used most extensively in the treatment of hook-worm infection, being given to adults in a dose of 3 cc. To children it is given in doses of 2 minims for each year of age up to fifteen years. Special preparation of the patient is not necessary unless there is marked constipation, when a laxative may be given. However, a light meal followed by a saline purge on the evening prior to the day of treatment is preferable. The drug may be given in divided doses but is commonly administered as a single dose. It may be enclosed in a hard gelatin capsule or in a fluid vehicle, usually water. Milk is also extensively used as a vehicle as it aids in forming an emulsion with the drug, thus covering up the taste. For this purpose, the dose of the drug is shaken up with a small quantity

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of milk and this emulsion is then poured into a larger quantity of milk. A saline purge one or two hours later followed by a warm soap-suds enema is recommended where feasible. Alcohol should be avoided both prior and for the day following therapy. The drug is contraindicated in alcoholics and those suffering from hepatic, renal, cardiac or pulmonary disease.

The use of carbon tetrachloride has been largely superseded by ethylene tetrachloride which is much less toxic and equally effective in the treatment of hookworm.

VII. TETRACHLORETHYLENE

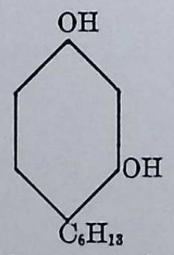
Tetrachlorethylene or ethylene tetrachloride ($CCl_2:CCl_2$) is less toxic and almost as effective as carbon tetrachloride in the treatment of hookworm. It is not readily absorbed and is believed to exert its anthelmintic activity by narcotizing the intestinal parasites.

Toxic effects consist of vertigo, headache and nausea. Alcohol and fats enhance its absorption and should be avoided for several days before treatment. After a saline purge on the preceding evening, the drug is administered in three 1 cc. gelatin capsules on an empty stomach. The dose for children is 3 minims per year of age. A saline purge is given within two hours or less after the drug and no food allowed until evacuation of the bowel occurs. The treatment should not be repeated within a period of three weeks.

When mixed infections of ascaris and hookworm occur, as is frequently the case, a course of treatment with hexylresorcinol should precede the use of tetrachlorethylene or carbon tetrachloride. Otherwise the stimulation of ascaris may lead to obstruction by a bolus of intertwined worms.

VIII. HEXYLRESORCINOL

This drug (1,3 hydroxy-4 hexylbenzene) was originally introduced as an antiseptic (p. 808). Lamson and his co-workers in an intensive study of the anthelmintic action *in vitro* of alkylhydroxybenzenes against pig ascaris found hexylresorcinol to be effective for this purpose. It was subsequently found to be an excellent remedy against human ascaris infection and to have also some action against hookworm.



Hexylresorcinol

Action.—The drug exerts an irritating action in both the stomach and intestine, but this is not severe. It is relatively non-toxic and may be administered to ambulatory patients and in repeated series of treat-

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ments if necessary. The drug is absorbed and eliminated in the urine, the remainder appearing in the feces.

Therapeutic Uses.—Hexylresorcinol is used chiefly in the treatment of ascariasis and as a preliminary therapy in the treatment of patients harboring both ascaris and hookworm. Purgation on the evening prior to treatment is desirable but not essential. The dose for adults is 1 gram (15 gr.) given in 5 capsules of 0.2 gram (3 gr.), on an empty stomach. Children receive 0.1 gram (1½ gr.) per year of age up to ten years. Glauber's salt is administered two hours after the drug and food is withheld from the patient for five hours. The treatment may be repeated after three days. Care should be taken that the capsules not be chewed to avoid erosion of the buccal mucosa.

IX. GENTIAN VIOLET

This dye which consists of a mixture of penta- and hexa-methylpararosaniline chlorides is also known as methylrosaniline, methyl violet or crystal violet. It is one of the antiseptic dyes (*cf.* p. 802) and is the drug of choice in the treatment of enterobiasis, strongyloidiasis and clonorchiasis.

Following its administration some patients may complain of dizziness, nausea, diarrhea, abdominal cramps, etc., but in therapeutic doses, the drug is relatively non-toxic. In the treatment of enterobiasis, two 0.03 gram (0.5 gr.) four-hour enteric coated tablets are administered three times a day for eight days. After an interval of one week this is repeated. For strongyloidiasis, the same dose of one and one-half hour enteric-coated tablets are administered for sixteen days. For children 0.005 gram (3/20 gr.) are given for each year of age. In cases refractory to oral therapy, transduodenal intubation of 25 cc. of a 1 per cent aqueous solution of the dye is often effective. In pulmonary strongyloidiasis the intravenous administration of 25 cc. of a 0.5 per cent aqueous solution is recommended.

X. PHENOTHIAZINE

Dibenzo-1,4 thiazine (thiodiphenylamine) or phenothiazine is used widely in veterinary medicine as an anthelmintic. It is a highly toxic drug which may induce acute toxic hemolysis. Nausea, vomiting, hematuria are other evidences of its toxic effects.

Phenothiazine is recommended for the treatment of enterobiasis in patients who are refractory or intolerant to gentian violet. The dose is 1 gram (15 gr.) per day for six days with repetition of the course of treatment after an interval of eight days. Children two to six years of age are given 0.5 gram (7½ gr.) for a similar period. The drug is also used in the treatment of dracunculosis (dragon or guinea worm infection).

XI. LECHE DE HIGUERON

The crude sap of the bastard fig, *fiscus laurifolia,* as well as of certain other wild fig trees contains a proteolytic enzyme, **ficin**, which acts as an effective anthelmintic by causing the digestion of the parasites. Where

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available it is the drug of choice in the treatment of trichuriasis. Following a saline purge on the preceding evening, 2 ounces of the drug are administered on an empty stomach followed by another saline purge in two to four hours.

PREPARATIONS

Aspidium

ASPIDIUM (U. S. P.), male fern, consists of the rhizome and stipes of Dryopteris filix-mas and yields not less than 6.5 per cent of the oleoresin.

FILIX MAS (B. P.), male fern or aspidium, consists of the rhizome and leaf-bases of Dryopteris filix-mas. Dose, 4 to 12 grams.

EXTRACTUM FILICIS (B. P.), extract of male fern or the Oleoresina aspidii, contains 25 per cent of filicin. Dose, 3 to 6 mil.

OLEORESINA ASPIDII (U. S. P.). The oleoresin of aspidium yields not less than 24 per cent of crude filicin. Dose, 4 grams.

Carbon Tetrachloride

CARBONEI TETRACHLORIDUM (U. S. P., B. P.), carbon tetrachloride, tetrachlormethane. Dose, U. S. P., 1 cc.; B. P., 2 to 4 mil.

CAPSULÆ CARBONEI TETRACHLORIDI (U. S. P.). Dose, 1 cc.

Chenopodium

OLEUM CHENOPODII (U. S. P., B. P.), oil of chenopodium, oil of American wormseed. A volatile oil distilled from the plant of Chenopodium ambrosioides var. anthelminticum. The oil yields not less than 65 per cent of Ascaridol ($C_{10}H_{16}O_2$). Dose, U. S. P., 1 cc.; B. P., 0.2 to 1 mil.

CAPSULÆ OLEI CHENOPODII (U. S. P.). Dose, 1 cc.

Gentian Violet

METHYLROSANILINÆ CHLORIDUM (U. S. P.), gentian violet, methyl violet, crystal violet, a dark green powder soluble in water. Dose, 60 mg.

Hexylresorcinol

HEXYLRESORCINOL (U. S. P.) ($C_{12}H_{18}O_2$), white needle-shaped crystals, practically insoluble in water. Dose, 1 gram.

Pomegranate

PELLETIERINÆ TANNAS (U. S. P., B. P.), a mixture in varying proportions of the tannates of four alkaloids (punicine, isopunicine, methylpunicine and pseudopunicine), obtained from pomegranate bark. Dose, U. S. P., 0.25 gram; B. P., 0.12 to 0.5 gram.

Santonin

SANTONINUM (B. P.) ($C_{15}H_{18}O_3$), a neutral principle derived from Artemisia pauciflora, is colorless when freshly prepared, but assumes a yellow color when exposed to the light. This does not seem to impair its activity materially, but it is preferable to avoid it by keeping santonin in amber-colored vials. Dose, 0.06 to 0.2 gram.

Tetrachlorethylene

TETRACHLOROÆTHYLENUM (U. S. P.), ethylene tetrachloride, C_2Cl_4, a clear, mobile liquid having a characteristic ethereal odor, practically insoluble in water. Dose, 3 cc.

CAPSULÆ TETRACHLOROÆTHYLENI. Dose, 1 cc.

Thymol

THYMOL (U. S. P., B. P.) ($C_6H_3C_3H_7CH_3OH$), occurs in common thyme and other plants, and forms large colorless crystals which have the odor of thyme

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and are very insoluble in water. It may also be prepared synthetically. The dose as an anthelmintic is: U. S. P., 2 grams, divided into 3 doses; B. P., 1 to 2 grams.

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PART V

Antiseptics and Disinfectants

VARIOUS balsams, tars and other aromatic bodies have enjoyed a reputation in the treatment of wounds since earliest antiquity but the whole course of surgery was changed about 1870 when Lister introduced the systematic application of antiseptics to wounded tissues. The general principle underlying this treatment was that infection arises from the invasion of the tissues by microörganisms and that it can be combated with by preventing them from reaching a wound or by retarding their growth on the injured surface by means of antiseptic drugs. The first of these which he introduced was carbolic acid, and this held its position unchallenged for several years, when it was discovered that many other substances were equally destructive to the microörganisms and were less poisonous to the invaded tissues. The Listerian principle of **antisepsis** was superseded by the present methods of preventing the infection of the tissues by a very careful technique **(asepsis)**. Only when this is impossible is the use of antiseptics and disinfectants still necessary. However, even the newer aseptic surgery depends on the use of disinfectants to cleanse the skin and instruments. During the first World War the study of the action of antiseptics and of antiseptic methods in surgery received a new impetus due, of course, to the unprecedented prevalence of infected wounds. As a result of these studies much valuable information was gained and some important modifications of established surgical antiseptic methods were introduced. During the second World War, on the other hand, the availability of the effective sulfonamide derivatives and antibiotics as systemic anti-infectives relegated interest in local antiseptics to minor consideration.

A **disinfectant**, in the strict use of the term, is a substance used to destroy microbes, whereas an antiseptic, while not actually killing the germs, prevents their growth as long as it remains in contact with them. A disinfectant is accordingly only intended to act for a short time, for if the infected matter be once rendered sterile it can only become dangerous by being again contaminated. For example, a room requires only to be disinfected after a case of infectious disease. A wound, on the other hand, even though completely disinfected may become contaminated again very easily and an antiseptic may be required to prevent the further growth of microbes. Many substances are disinfectant in large quantities and antiseptic in more dilute solutions, but others are too weak to disinfect thoroughly though they retard the growth of pathogenic organisms, and still others may be employed to disinfect but are unsuitable for use as antiseptics, either because they are too poisonous to be applied for a sufficient time, or because they lose their activity on contact with living matter (*e. g.*, oxidizing disinfectants).

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A very large number of substances possess disinfectant properties, that is, are capable of destroying microbes when they can be applied in sufficient quantity. They have no specific action on the microbes, however, but act as general protoplasmic poisons, destroying living tissue of all kinds wherever they come in contact with it. On the other hand, drugs such as strychnine, which act on specialized parts of the vertebrate organism and have less effect on the less differentiated tissues, are equally harmless to the undifferentiated protoplasm of the microbes. It is of importance to note that the ordinary antiseptics do not act more strongly on microbes than on the tissues in which they are embedded or on the phagocytes with which the organism is combating the infection. The destruction of the septic organisms in a wounded surface entails the destruction of the surrounding cells also. Thus disinfection can only be carried out in a part in which the superficial cells are not of vital importance and may be restored by new growth. It is therefore impossible to disinfect the tissues of the body as a whole unless a drug is parasitotropic, that is, has a specific affinity for the parasite rather than for the organs in general (organotropic). Although many attempts were made to find drugs manifesting such selectivity it was only with the introduction of the sulfonamides, antibiotics and other systemic anti-infectives that this goal was attained. By the local or systemic application of these substances antisepsis may be obtained without injury to the normal tissues. The term antiseptic is now usually limited to the drugs exerting a local anti-infective action although in its broad sense it should also include the systemic anti-infectives described in previous sections.

The antiseptics and disinfectants act upon most forms of living matter, and in many instances their effects are obviously due to their possessing powers of oxidizing or of coagulating proteins. In some instances their effectiveness is probably due to interference with basic enzyme systems, or to their interference with permeability of the vital membrane surrounding the pathogenic organisms. The amount of destruction induced varies with the degree to which the poison penetrates the tissues to which it is applied. For example, mercuric chloride diffuses deeply into tissues brought in contact with it and causes wide destruction, while the oxidizing disinfectants lose their efficacy on meeting proteins and thus affect only the most superficial cells. If microbes were confined to the surface, the latter would be sufficient for their destruction, but in order to disinfect a wound it is necessary to penetrate more deeply and thus efficient disinfection implies a certain amount of destruction of the tissues in which the microbes are harbored. This local destruction of cells and nervous structures induces pain and irritation and many efficient disinfectants are irritants. Their action as irritants arises from the same qualities as their disinfectant power, namely, from their general toxicity to living matter.

When a surface has been poisoned by means of disinfectants, it heals less quickly, and this had led to the more sparing use of antiseptics and to the development of the aseptic method, in which organisms are excluded instead of being admitted and then destroyed. With the

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discovery of the sulfonamides and antibiotics these, in turn, displaced the previously used antiseptics in many cases for these substances not only inhibit the growth of the invading pathogens but induce only minimal or no injury to the normal tissues.

In addition to their local effect, many of the antiseptic and disinfectant drugs have a further poisonous action when they are absorbed and circulate in the blood, and this has led to a further limitation of their use. This general action does not necessarily arise from the qualities which render them antiseptic, and may be avoided by care in the choice of the drug and in its use.

The action of different drugs upon the microörganisms varies in nature in the same way as the action on other living cells. Some apparently penetrate into the interior by virtue of their solubility in lipids, and this penetration is facilitated by anything which decreases their solubility in the surrounding medium. Others accumulate on the surface of the organisms by adsorption, so that the microbe is surrounded by a dense layer of disinfectant. Yet others appear to enter into true chemical combination with the constituents of the parasites. Some of the antiseptics (*e. g.*, carbolic acid) enter the cell by simple diffusion and do not accumulate in its interior in greater concentration than in the solution surrounding it. Others (*e. g.*, corrosive sublimate) tend to accumulate in the cell and on its surface by adsorption, and thus are withdrawn from the solution if a sufficient number of microbes is present.

The efficiency of any disinfectant naturally depends on the concentration in which it comes in contact with the microbes and the time during which it remains in contact with them. Thus a solution of mercuric chloride of the strength of 1 in 3,000 is much more efficient than one of 1 in 10,000, and after exposure to a solution for five minutes far fewer microbes escape than after exposure for two minutes. Another factor is the temperature at which the microbes are exposed to the disinfectant, for it is found that when the latter is kept at about 30° C. far fewer bacteria escape than when ordinary room temperature prevails. Different species of microbes vary in their resistance, and different cultures of the same microbe and even different individuals of the same culture exhibit marked variations in susceptibility. The effect also often varies inversely with the number of microbes present, because each of these withdraws a certain amount of the disinfectant and thus reduces the general concentration of the solution. And other proteins have the same influence as the microbes themselves, for they offer the disinfectants the same surface for adsorption or combine with some of them in the same way as the proteins of the microbes. Thus a concentration which is sufficient to sterilize water infected with bacteria, may have little or no effect if applied to a suppurating wound, because the greater part of the disinfectant is taken up or otherwise rendered inactive by the proteins of the secretion, leaving only a low concentration to act on the microörganisms. Thus many substances which are powerful disinfectants in ordinary fluids lose their activity in protein solutions (commonly called the "protective action of colloids"), owing to their forming combinations with the proteins, so that though they are not

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dangerous to the host, they are comparatively innocuous to the microbes in the tissues. The inhibiting action of the proteins may also be due partly to their limiting the diffusion of the disinfectant. In fact, many of the antiseptics and disinfectants act on proteins generally and not specifically on microbes. The lipids, like the proteins, may also lower the potency of antiseptics.

If a poison is to penetrate into the interior of an organism in quantity, it must be as soluble in the protoplasm as in the fluid in which it is applied, for it is obvious that it will not leave a medium in which it is readily soluble for one in which it is dissolved with difficulty. Accordingly, it is found that fats and oils in which the members of the aromatic series are very soluble are not suitable as media for their application, for the poisons remain in the oily menstruum and fail to penetrate the microbes in which they are less soluble. Mercuric chloride dissolved in alcohol has little germicidal power but this is due to the fact that mercuric chloride, and indeed salts of the other heavy metals as well, are not dissociated in alcohol (95 per cent) and it is necessary in order that the salt be active that it should be so dissociated. On the other hand, if the mercuric chloride (or silver nitrate) is dissolved in dilute alcohol (25 per cent) its action is strengthened, probably due to the penetration of the salt being favored. The addition of inorganic salts to an aqueous solution of carbolic acid often increases its antiseptic power, because the poison becomes less soluble in the water and shows a greater tendency to escape from it into the interior of the microbes.

There is reason to believe that solutions containing several disinfectants are more strongly antiseptic, than those containing an equal percentage of the individual pure bodies; for example, a mixture of phenol and mercuric chloride, is more efficient than a much stronger solution of either alone; a combination of gentian violet and acriflavine ("acri-violet") is more germicidal than either alone.

Disinfectants and antiseptics are used for a large variety of purposes and it may be well to consider the principles which underlie their uses before discussing the special features of each drug.

1. **In Surgery,** Lister advised that not only infected wounds should be treated with disinfectants but that infection of any wound should be guarded against by the application of antiseptics which would retard the growth of microbes. It is now recognized, however, that a clean wound requires no antiseptics and heals more quickly if they are avoided. Disinfection in surgery is now applied only to tissues already the seat of infection, and to objects which may come in contact with a clean wound. Among the latter, those which offer the greatest difficulty are the skin of the patient and of the operator, and a large number of drugs have been employed to disinfect these and render them harmless. Among the disinfectants more commonly used to disinfect the skin or to destroy the organisms in a wound already infected are soap and other detergents; the carbolic acid group, aqueous ethyl, propyl or isopropyl alcohol; acetone; the inorganic and organic mercurials; the oxidizing disinfectant group, including iodine and other halogens and their derivatives, etc. For use in disinfecting the skin in certain loca-

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tions which are especially difficult to render sterile, such as the perianal region, Bonney and Browning have found that a mixture of crystal violet and brilliant green (violet-green) in a 1 per cent solution is especially effective. The disinfectant must be applied in solution or suspension in water, and should induce as little irritation as is compatible with its fulfilling its purpose. This is of special importance in dealing with the delicate, sensitive mucous membranes such as the eye, which cannot be subjected to such treatment as would be necessary in other parts of the body. A danger which is smaller now than formerly is from the absorption of the disinfectant giving rise to general poisoning. This arose as a general rule not only from the drug applied during the operation, but also from its too lavish use in the subsequent dressings and the use of powerful disinfectants to wash out large abscesses, the uterus, or other organs.

Instruments, ligatures, etc., are generally disinfected by heat, but are often kept in dilute solutions of carbolic acid or other disinfectants until required.

The relative disinfecting power of the drugs used in surgery has been investigated repeatedly but no satisfactory ratio can be given as yet, because it is impossible to imitate the conditions in a septic wound closely enough in experimental determinations. And estimations of the relative power in destroying organisms in water or in broth cultures depend upon a variety of conditions, such as the number of organisms and the completeness with which the disinfectant is removed before test growths are made.

For disinfection of the skin 70 per cent ethyl alcohol, the mixture of ethyl and propyl alcohol, or acetone are quite efficient, especially if the skin is rubbed with gauze at the same time that these liquids are being used. The solutions containing iodine, such as the mild tincture of iodine U. S. P., hold high rank as surgical disinfectants of the skin although their use is limited by their staining and irritating properties. In the case of mucous membranes the silver compounds are extensively used.

2. **In the Treatment of Skin Diseases,** a number of disinfectants have been employed, and where the area of infection is small it may be permissible to use the more powerful ones if necessary. But in widespread disease the dangers of local irritation and of absorption preclude all except the least noxious, and it remains a question how far these act in retarding the growth of an infecting organism, and how far their effects may be due to their causing slight irritation and improved nutrition. Some dermatologists hold the view that these mild skin remedies owe much of their value to their reducing properties. Among the remedies used are chrysarobin, pyrogallol, resorcinol, salts of mercury and the tar series.

3. **To Disinfect the Intestine.**—Septic processes may occur either in the contents of the intestine or in its walls, the former affecting the general organism only by the production of poisonous or irritant substances which may be absorbed, while in the latter the tissues of the wall themselves become the seat of active disease. The older attempts

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to sterilize the intestinal tract proved futile, it being generally conceded that it was better to remove the putrefying contents by means of a purgative, than to attempt to render them sterile in the bowel by means of disinfectants. By the use of the sulfonamides it is possible, as we have seen, to effect partial sterilization of the gut. When the bowel wall itself is the seat of bacterial infection the use of systemic anti-infectives is necessary and it is probable that some of the newer antibiotics will ultimately furnish the long sought effective intestinal antiseptic.

Any drug used for the disinfection of the intestine must not be irritant, nor very poisonous. It must not be too soluble, since otherwise it may be absorbed from the upper part of the bowel, and on the other hand it must be soluble to some extent, or it cannot mix very intimately with the contents of the intestine.

4. **To Destroy Pathogenic Germs in the Tissues After Absorption.**—To destroy all forms of bacteria in the tissues, while leaving the host uninjured, a drug must possess properties which will exert a specific action upon the invading organism with only tolerable effects on the host. Such a specific action is seen in the effects of the antimalarials, sulfonamides, antibiotics and other systemic anti-infectives described in previous sections.

5. **In the Treatment of Septic Genito-urinary Diseases.**—Good results are obtained in infection of the genito-urinary tract through which many of the antiseptics are eliminated from the body. In the course of their elimination they are concentrated; thus a quantity of disinfectant which is inactive when distributed through the protein-rich tissues of the body, may very well be efficacious when it is dissolved in the comparatively small quantity of the urine, and especially since here it finds no protein to combine with except that of the tract through which it passes. The drugs used for this purpose must not be too irritant to the mucous membranes of the alimentary tract, and must be easily absorbed and not dangerously poisonous.

In addition to the administration of drugs for the purpose of disinfecting the urine and the urinary tract, an effort has been made to render the urine sterile by means of its acidification produced by the giving of a ketogenic diet. This method of rendering the urine more acid is roundabout and clumsy and has been superseded by the use of mandelic acid—a relatively non-toxic, hydroxy acid, excreted unchanged in the urine which it renders bacteriostatic.

In addition to the oral method of treatment, antiseptics and disinfectants may be applied by injection into the urethra and bladder by the ordinary surgical procedure. For this purpose the silver compounds, potassium permanganate, chloramine and acriflavine, were formerly extensively employed but these have been largely superseded by the administration of the sulfonamides and antibiotic drugs.

6. **In the Treatment of Infections of the Lungs and Other Internal Organs and Their Secretions.**—Traces of some of the more volatile antiseptics are eliminated in the breath, and this suggested their internal use to destroy microbes in the lungs, especially the tubercle bacillus. However,

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the case of the lungs differs entirely from that of the kidney, for in the former there is no concentration of the disinfectant in the organ, but it is excreted in even greater dilution than that in which it circulates in the general tissues; the surface of the lungs has been estimated at about 70 square meters, and it is impossible to conceive that small quantities of antiseptic spread over this surface can affect bacteria harbored on it. It is only with the introduction of the recent sulfonamide and antibiotic drugs that efficient sterilization of infections of the lungs as well as other internal organs and their secretions has been attained.

7. **To Disinfect Rooms, Furniture, Clothing, Excrementa,** the strongest and cheapest drugs which are available are employed. It is quite futile to attempt to carry out such disinfection unless with concentrations which would be immediately fatal to all higher organisms. For rooms and furniture, formaldehyde or sulfur dioxide are best adapted as they are volatile and penetrate fairly well, but the latter bleaches all dyed material. The use of ultraviolet irradiation or of relatively non-toxic antiseptics dispersed in aerosols has also been recommended for the sterilization of the atmosphere particularly in surgical operating rooms. Clothes are best disinfected by washing or preferably by steam or dry heat, or formaldehyde solution may be employed. Excrement may be disinfected by chlorine or lime; crude carbolic acid and tar are less certain, and the oxidizing disinfectants are expensive when used in quantity.

8. **To Disinfect Drinking-water.**—The water supplies of urban areas are disinfected when necessary by the use of chlorine and filtration. Smaller quantities may be freed from infectious organisms by heat or filtration, but when these are not available, chemical disinfection may be necessary, as for example in military expeditions. The disinfectant must not be present in such quantities as to render the water poisonous, or even disagreeable to the taste. Fortunately, the organisms are not protected by the presence of colloids and are therefore destroyed by very small quantities of disinfectants. The most convenient is chlorine which may be used in the form of the hypochlorite, halazone (p-sulphonedichloramidobenzoic acid) or succinchlorimide.

Many antiseptics and disinfectants are used for a variety of purposes and might be classed under several of these headings. The following arrangement is therefore an arbitrary one, and merely points to the use for which the drug has been considered most adapted. Many of the drugs to be discussed are obsolete insofar as their therapeutic usefulness is concerned. However, they are still widely used and remain of pharmacological and toxicological interest.

I. SURGICAL ANTISEPTICS AND DISINFECTANTS

1. Soaps and Other Detergents

Ordinary soaps may be used to effectively rid the skin of bacteria. They act in virtue of their detergent effects being designated as anionic detergents since the effective part of the soap molecule is an anion.

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Recently other detergents which are cationic have been introduced as antiseptics. They are mixtures of alkyl chlorides.

Zephiran chloride is a mixture of alkyl dimethylbenzyl ammonium chlorides having the general formula $C_6H_5CH_2N(CH_2)_2RCl$ in which R represents a mixture of alkyl radicals from C_8H_{17} to $C_{18}H_{37}$. It is used for the prophylactic disinfection of the intact skin and for the treatment of superficial injuries in the form of the 1 : 1,000 tincture. For application to mucous membranes and for irrigations, more dilute solutions of 1 : 2,000 to 1 : 40,000 are employed.

Phemerol, para-tertiary-octyl-phenoxy-ethoxyethyl-dimethyl benzyl ammonium chloride, is another detergent used in the form of a tincture, alcohol-acetone solution, or in the form of its aqueous solution for disinfection of the skin.

2. Alcohols

Ethyl alcohol is a disinfectant when used in 70 per cent dilution by weight or 78 per cent by volume, and has been used to clean and disinfect the skin and hands before operation. The disinfectant action diminishes rapidly as this strength is departed from either by dilution or by use of more concentrated solutions. Normal propyl alcohol has also considerable disinfectant power and a mixture of 95 per cent ethyl alcohol (675 cc.) with pure propyl alcohol (250 cc.) and distilled water (250 cc.) prepared at 25° C. has been shown to be more effective as a skin disinfectant than ethyl alcohol alone. The disinfectant action of alcohol can be aided to a considerable degree by gently rubbing the skin with sterile gauze while the alcohol is being employed.

Isopropyl alcohol has also been recommended for the disinfection of the skin and of hypodermic syringes and needles. It is also employed as a disinfecting agent prior to the administration of insulin. Although it compares favorably with ethyl alcohol insofar as its anti-infective action is concerned, neither these alcohols, nor most of the other commonly used antiseptics can be relied on to destroy the spore-bearing organisms.

3. Carbolic Acid (Phenol)

Carbolic acid, or **phenol**, the first of the modern antiseptics to be introduced, acts like the rest of the simpler benzol compounds as a **General Protoplasm Poison**, although in the vertebrates it affects the central nervous system more powerfully than the other tissues.

Its poisonous effects are well seen when it is applied to unicellular organisms, such as the *protozoa*. Even dilute solutions cause immediate arrest of all movements; the organism assumes a spherical shape and loses its transparency, and, unless the solution be very attenuated, dies in the course of a few minutes. *Plant cells* are acted on in the same way, and the individual cells of more highly organized animals, such as the *ciliated epithelium* of the air passages and the *spermatozoa*, are killed at once when brought in contact with carbolic acid. There is some evidence, however, that very dilute solutions of carbolic acid, as of other antiseptics, tend to increase the activity of protoplasm, for while solutions of phenol, such as are used as surgical antiseptics, are

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immediately fatal to the yeast plant, very dilute solutions increase its activity. The effect of carbolic acid on protoplasm has, however, been studied chiefly in the *bacteria*. Its antiseptic power, while always considerable, is found to vary greatly with the species of microbe. Thus, while it is fairly poisonous to the ordinary pyogenic organisms, it has to be present in very concentrated form to destroy the more resistant spores of anthrax, and like other antiseptics, is much less poisonous to the microbes than to the protozoa and other simple forms of life. The development and reproduction of many microörganisms have been found to be much delayed, or altogether prevented, as long as they remained in a solution of 1 part of carbolic acid in 400 to 600 parts of water, but in order to kill them very much more concentrated solutions (5 per cent) were required, and Koch found that the spores of the anthrax bacilli were destroyed by 5 per cent carbolic solution only after they had remained in it for two days.

Carbolic acid precipitates **Proteins** in solution and also in the cells. It does not seem to enter into any firm combination with them, for it can be washed out of the precipitate with comparative ease. It results from this that carbolic acid penetrates more thoroughly than the metallic antiseptics, which are rendered insoluble by the protein they meet, and whose action therefore tends to remain confined to the surface.

This coagulation of the proteins occurs whenever carbolic acid is brought in contact with the tissues. On the **Skin** a white, opaque lesion is formed by concentrated phenol, which becomes red and shining afterward and then falls off in a few days, leaving a light brown stain which may remain for several weeks. Even a 5 per cent solution applied to the fingers produces tingling and warmth, which is often followed by opacity and shrinking of the epidermis and a sense of numbness. This numbness may amount to almost complete anesthesia if more concentrated solutions are applied, no pain being felt even when the skin is cut through. When applied for some time and prevented from evaporating, carbolic acid may cause extensive dry gangrene of the part, from its penetrating through the surface layer and reaching the deeper tissues. Applied to a **Wound** in 5 per cent solution, phenol induces pain and irritation followed by local anesthesia, and a white pellicle of coagulated proteins is formed. It causes irritation and necrosis of the **Mucous Membranes**, and if applied in sufficient quantity may lead to sloughing and acute inflammation. This local effect may prove fatal from shock and collapse when large quantities of the undiluted acid are swallowed, the effects resembling exactly those produced by other corrosive substances. Carbolic acid is rapidly absorbed from the stomach and bowel, but after some time the absorption is much slowed owing to local changes in the vessels of the intestine.

Toxicology.—In *man* delirium and excitement have been observed in some cases, but convulsions are comparatively rarely seen. When large quantities are taken, immediate unconsciousness may result and death follow within a few minutes. How far this is due to the local corrosion, and how far the direct action on the central nervous system is involved, cannot be determined. In more gradual poisoning, depression and weakness, headache, nausea and vomit-

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ing are followed by giddiness, noises in the ears, pallor and collapse, with irregular pulse and respiration, and cold perspiration; fainting and unconsciousness then lead to failure of the respiration and death. Fatal poisoning may arise from swallowing a concentrated or a dilute solution, or from absorption from wounds and abscesses. It has also occurred in man from absorption through the unbroken skin.

The autopsy sometimes gives no special indications of the cause of death, save the local corrosion of the alimentary canal. Inflammation and necrosis of the intestine is said to have been observed in some cases in which the poison was absorbed from skin wounds, and fatty degeneration is sometimes induced in the liver and the renal epithelium, but is not constant.

In the *frog* carbolic acid first causes depression and loss of the spontaneous movements, and later fibrillary twitching in the muscles, augmented reflex excitability and finally tonic convulsions. These may last for some time and then complete paralysis of the central nervous system supervenes, while the heart and the peripheral nerves and muscles remain active. A dilute solution of carbolic acid applied directly to the exposed spinal cord paralyzes the sensory elements immediately, while leaving unaffected the motor fibers and the cells of the anterior horn (Baglioni).

In *mammals* very similar symptoms are produced, save that there is often no noticeable preliminary stage of depression. Some weakness and lethargy may be present, however, and is followed by marked muscular tremor, which resembles the shivering produced by cold. At intervals this is interrupted by sudden twitches in different muscles, and later by clonic convulsions. The respiration and pulse are at first accelerated, but afterward are slow, irregular, and weak. The movements become feeble and appear at longer intervals, the respiration is shallow and irregular, and the animal passes into a condition of collapse, in which, however, the sensibility to pain is often preserved. Eventually death occurs from asphyxia. After very large doses the collapse may be immediate, no convulsions being observed, the heart and respiration often ceasing simultaneously. In most cases salivation is a marked symptom, and the temperature often falls far below the normal.

Central Nervous System.—The convulsions in the frog arise from increased irritability of the spinal cord, especially of the anterior horn cells, for they are not arrested by section of the medulla oblongata. In mammals the sudden contractions of isolated muscles appear due to a similar action on the spinal cord, but the clonic convulsions and the persistent tremors are probably of cerebral origin. The rarity of convulsions in man has not been satisfactorily explained. In some cases the course of the intoxication is too short, the large amount of poison swallowed inducing immediate collapse, while in others their absence may be due to the debility of the patient from disease; but in a considerable number of cases of poisoning in which neither of these conditions was present, no convulsions were observed. The primary stimulation of the central nervous system in animals is followed by depression and paralysis if large doses are administered.

The acceleration of the **Respiration** and of the **Heart** seen in mammals has been supposed to be an indirect result of the increased muscular movement and convulsions, but this seems to be incorrect, for the heart is found to be accelerated before the convulsive movements and tremor appear, and the frog's heart is accelerated in cases where no movements whatever occur. It would seem probable that the acceleration of the heart is due to direct action on the muscle or on the regulating nerves. The subsequent slowing is undoubtedly due to muscular action.

The acceleration of the respiration precedes the increased movement, and would therefore seem to be due to action on the medullary center, which is first stimulated and later paralyzed. The vasomotor center is depressed by the injection of carbolic acid into the blood, and this, together with the weakness and slowness of the heart, causes a fall in the blood-pressure and collapse.

The peripheral **Nerves and Muscles** do not seem to be affected in general poisoning in mammals, although in the frog their irritability and the capacity for work of the muscle may be somewhat reduced.

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On the direct application of solutions of carbolic acid to the nerves or muscles, these are killed at once, like other forms of living matter; even dilute solutions paralyze the nerve fibrils and terminals and thus induce local anesthesia.

The increased **Secretion** of saliva, perspiration and tears which is seen in poisoning in mammals is probably of central origin, and may possibly be associated with the nausea and vomiting.

The fall in **Temperature** in carbolic acid poisoning seems, for the main part, to be due to the collapse, although it is impossible to state how far this may be aided by some alteration of the regulating function, such as is seen in the closely related group of the antipyretics.

Carbolic acid added to the defibrinated **Blood** leads to the slow formation of methemoglobin, but this does not occur in the living animal. Occasionally some destruction of the red blood cells is caused in animals through the injection of carbolic acid directly into the blood-vessels, and in one case of poisoning in man hemoglobin was detected in the urine, indicating that some of the red cells of the blood had been destroyed.

Excretion.—Some of the carbolic acid absorbed is oxidized to hydroquinone and pyrocatechin, and these and also the unaltered carbolic acid are excreed in the urine in combination with sulfuric and glycuronic acids. The hydroquinone and pyrocatechin tend to become further oxidized to colored substances and the urine therefore assumes a dark, dusky-green color which may change to brown or even black. This change may occur in the body, and the urine is very often passed of a greenish-brown color, but further oxidation takes place on exposure to the air, resulting in deeper coloration which commences at the surface of the fluid and gradually extends downward. The depth of the shade depends not on the amount of phenol sulfate in the urine, but on that of the dioxybenzols, and a darker urine is often observed, therefore, when the absorption has occurred from an open wound (in which the conditions are especially favorable to oxidation) than from much larger quantities absorbed from the alimentary canal.

The presence of glycuronates in the urine may lead to its reducing Fehling's solution, and thus give rise to the suspicion of glycosuria. On the other hand, the passage of these bodies through the kidney often causes some irritation and albuminuria. The double sulfates of the urine are, of course, much increased, and the inorganic sulfates are correspondingly diminished.

Therapeutic Uses.—Carbolic acid is used as an antiseptic in surgical operations in 2 to 5 per cent solution in water. It now plays a much less important rôle in surgery than it did in the first days of antisepsis; in fact it is now employed only to protect the instruments from infection. Its irritant action and the danger of absorption have also rendered it obsolete as a dressing or lotion after operations or injuries, where there is any large absorbent surface, or where irritation is liable to be injurious, as in most forms of skin disease.

Certain proprietary salves which contain phenol are widely sold for application to burns, boils and other painful lesions of the skin. Their

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popularity is probably dependent upon the anesthetic action of the phenol which they contain. The applications of such salves or dilute solutions of phenol in bandages to injured fingers for a number of days has led to gangrene, necessitating amputation (Harrington).

Carbolic acid has a limited use as a caustic in the form of the liquefied preparation, and is less painful than most other caustics. It has also been employed in itching skin diseases.

Poisoning.—In carbolic acid poisoning, when it has been taken by the mouth, the first treatment is the removal of the poison by the stomach tube and the thorough lavage of the stomach with water to which 10 per cent of alcohol may be added; the alcohol dissolves the poison more readily than water and thus facilitates its removal, but has no other antidotal action, and should be removed from the stomach as completely as possible; when absorption has occurred from the skin or from a wound the dressing should be removed at once. When coma and collapse set in, the patient is to be sustained by the application of warmth externally, and by the administration of such central nervous stimulants as caffeine or strychnine; artificial respiration may eventually be used, although there is little prospect of resuscitation if the intoxication has advanced so far. The corrosion induced by carbolic acid locally may be treated by washing the part with alcohol, which dissolves the acid readily.

PREPARATIONS

U. S. P.

PHENOL, carbolic acid, forms colorless, deliquescent crystals when recently prepared, but often assumes a reddish tinge from oxidation. It has a characteristic odor and is intensely corrosive. It is soluble in about 15 parts of water, but becomes liquid when 10 parts of water are added to 90 of the crystals, forming PHENOL LIQUEFACTUM of the U. S. P. This must be carefully distinguished from the ordinary solution of carbolic acid, which contains only 2 to 5 per cent of phenol, while the liquefied carbolic acid contains from 80 to 90 per cent.

PHENOL LIQUEFACTUM contains 88 per cent of phenol.

UNGUENTUM PHENOLIS, 2 per cent phenol in yellow ointment.

B. P.

PHENOL.

GLYCERINUM PHENOLIS, 16 per cent phenol. Dose, 0.3 to 1 mil.

PHENOL LIQUEFACTUM, 80 per cent phenol. Dose, 0.06 to 0.2 mil.

TROCHISCUS PHENOLIS. Each lozenge contains 0.03 gram of phenol.

SUPPOSITORIUM PHENOLIS. Each suppository contains 0.6 gram of phenol.

UNGUENTUM PHENOLIS, 3 per cent phenol.

4. Substituted Phenols

A number of phenol derivatives are used as antiseptics. In general, these are more bactericidal than phenol itself and are less caustic and toxic. Thus the halogenated phenols, in which a halogen is substituted for one or more of the hydrogen atoms of phenol are much more poisonous to microörganisms than the original substance, while their toxicity in mammals is not increased in the same ratio. The antiseptic activity of the halogenated phenols is greatest in the case of the chlorophenols, less in the bromophenols and least in the iodophenols. In the case of the monohalogen derivatives, the meta derivative is most active; the

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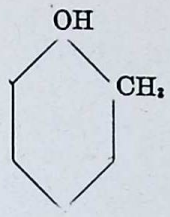
ortho, the least active. Dihalogenated compounds are more effective than the monohalogenated ones. Because of their insolubility the halogenated phenols have found little use in medicine. On the other hand, the alkyl and hydroxy derivatives of phenol have largely displaced the parent compound.



Orthocresol

The **cresols** or cresylic acids, which are methyl derivatives of phenol, have been substituted for carbolic acid to a considerable extent. There are three isomeric cresols which all resemble carbolic acid closely in action, and which present only minor points of difference from each other. Metacresol is said to be less poisonous and less irritant than carbolic acid, while it is credited with a more powerful antiseptic action; orthocresol, on the other hand, is said to be more dangerous than carbolic acid, and paracresol to be the most poisonous of all. But the differences in toxicity between the cresols are too small to be of practical importance, and their germicidal action is approximately equal when they are used in suspension with soaps, as is usually the case.

Many cases of suicidal poisoning with cresol preparations have occurred and have presented symptoms similar to those of carbolic acid poisoning—collapse and exhaustion followed by coma and death; in some cases marked alterations have been found in the liver along with nephritis and hemolysis. Much of the cresol absorbed undergoes complete oxidation in the tissues, but about one-third of that ingested is excreted in the urine in combination with sulfuric and glycuronic acids.

The cresols are constituents of tars and other crude disinfectants. In pure form they are only slightly soluble in water, and it has been found necessary to form them into emulsions or suspensions for surgical use. A large number of these cresol preparations are available and differ chiefly in the way in which they are suspended in water (*creolin, solveol, solutol, lysol*). These preparations are not devoid of poisonous properties, as is often stated; on the contrary they are little if at all less dangerous than carbolic acid. Their germicidal action has been overrated by some authorities and has been denied by others. On the whole they appear to be more powerfully antiseptic than carbolic acid when they are used in emulsion form; their insolubility in water facilitates their passage into the bacteria, in which they are more soluble; and the emulsion form has a further advantage as the fluid coming in contact with the bacteria must always be saturated with the antiseptic. In spite of these facts recent work has indicated that the disinfectant effect on the skin is not as powerful as would be expected from the results obtained in the test-tube.

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The cresols are used principally for disinfecting inanimate objects for which purpose they are cheaper and more effective than phenol. Proprietary preparations are widely advertised as vaginal douches but the advisability of their use for this purpose is questionable.

Cresatin, the acetic acid ester of metacresol is less toxic than cresol retaining its antiseptic and analgesic properties. It is recommended for application to the inflamed mucous linings of the ear, nose and throat.

Triorthocresyl Phosphate.—In 1930 a peculiar form of flaccid paralysis (ginger paralysis) appeared in various parts of the United States. After a careful study this was shown to be due to the presence in certain lots of fluid extract of ginger of triorthocresyl phosphate. The paralysis in most cases affected adult males who gave a history of having partaken of the beverage some five to ten days before the muscular symptoms developed. The immediate effects after taking the fluid extract were merely those of alcoholic intoxication accompanied at times by evidences of gastro-intestinal irritation. About ten days later soreness of the leg muscles was noticed and some numbness of the fingers and toes. Paralysis of the toes followed, succeeded shortly by bilateral foot-drop. Weakness of the fingers and wrist-drop occurred later, but the symptoms on part of the upper extremities were never so marked as they were of the lower. The paralysis affected the victims with all degrees of severity from slight disability to practically complete helplessness, the patient being confined to bed and even unable to feed himself. There were few or no sensory disturbances.

Laboratory studies have shown that a similar set of symptoms can be produced in certain species by the administration of the triorthocresyl phosphate. The symptoms are especially characteristic in chickens in which flaccid paralysis of the legs is often followed by some weakness in the wings. In the cat and dog paralysis is marked in the hind legs while the fore legs may not be so much affected. Similar paralytic manifestations have been produced in calves and in monkeys. Chemical examination of the adulterated fluid extract were in harmony with the pharmacological findings in showing that the offending compound was present to the extent of about 2 per cent. It appears that the neurotoxic property of the compound does not reside in the cresol portion of the molecule but in the entire cresyl phosphate aggregate. Triorthocresyl phosphite and triphenyl phosphate resemble the triorthocresyl phosphate closely in that they are also neurotoxic, possessing a delayed action. However, in the case of the triphenyl phosphate the process is more diffuse and the paralysis, therefore, more generalized. In the case of triorthocresyl phosphite certain paths in the spinal cord are affected in addition to the peripheral motor nerves. In general the phenyl ester seems to affect more particularly the motor nerve cells while the cresyl compounds exert their action upon the myelin substance of the conducting fibers—peripherally in the case of orthocresyl phosphate and centrally as well as peripherally in the case of the phosphite, which produces degeneration of certain tracts in the spinal cord. The phosphoric ester is more restricted in its effects while the phosphorous compound is more diffuse and generalized.

Preparations

Cresol (U. S. P., B. P.), a mixture of the three cresols, forms a colorless or straw-colored fluid with a phenol odor. Soluble in 60 parts of water. Dose, B. P., 0.06 to 0.2 mil.

Liquor Cresolis Saponatus (U. S. P., B. P.). Cresol, 50 per cent, suspended in water by means of soap, is used diluted to about 2 per cent as a surgical disinfectant.

Chlorocresol (B. P.), parachlorometacresol, 6-chloro-3-hydroxytoluene.

Chloroxylenol (B. P.), parachlorometaxylenol, 2-chloro-5-hydroxy-1:3-dimethylbenzene.

Liquor Chloroxylenolis (B. P.), solution of chloroxylenol, roxenol.

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5. Other Aromatic Surgical Disinfectants

Many other members of the benzene or aromatic series have enjoyed a more or less transient reputation as surgical disinfectants and antiseptics. Thus *Thymol* ($C_6H_3CH_3C_3H_7OH$), obtained from oil of thyme, was used to a limited extent as an antiseptic lotion in $\frac{1}{10}$ per cent solution and also as a mouth wash and gargle, but in this strength it is only feebly active and it is too insoluble in water to form a really effective germicide.

Salicylic acid and **sodium salicylate**, which have already been considered in an earlier chapter (p. 687), were at one time used as antiseptic washes in surgery, and indeed promised to supplant carbolic acid for this purpose as they are less irritant and less poisonous. The acid is destructive to the pyogenic microörganisms suspended in water but has much less effect than carbolic acid when proteins are present, and its use as an antiseptic has been abandoned in practice by most surgeons.

Picric acid or trinitrophenol, $C_6H_2(NO_2)_3OH$, has been used as an application to wounds or burns in the form of a saturated watery solution (1 per cent) on lint. It has approximately the same disinfectant action as carbolic acid, but enters into a more stable combination with proteins and is thus slightly astringent. Larger quantities are irritant and in some cases have given rise to gastro-enteritis and nephritis; the skin and mucous membranes are stained yellow even when the picric acid is carried to them in the blood, and this coloration has sometimes been confused with jaundice. Violent convulsions occur sometimes, in other cases, collapse. The urine is yellow or red and contains casts, but little albumin and no bile, the absence of the latter serving to distinguish the condition from jaundice; picric acid tends to destroy the red blood cells in animals but no marked fall in these has been observed in man. It is excreted as picramic acid ($C_6H_2OHNH_2(NO_2)_2$) in the urine.

6. Mercuric Chloride and Other Inorganic Mercury Compounds

Soon after the treatment of wounds with carbolic acid was established, its rival, corrosive sublimate, was introduced as a more powerful disinfectant. There is no question that the claim was justified and that corrosive sublimate in ordinary surgical practice has greater germicidal and antiseptic powers than carbolic acid. At the same time bacteria must be exposed for a longer time to its action before they are destroyed, and it has a more injurious effect on the tissues with which it comes in contact and is more poisonous when it is absorbed. A certain amount of mercury remains attached to the proteins of the microbes and restrains their reproduction even when it does not actually kill them; owing to this fact corrosive sublimate has been credited with greater disinfectant power than it merits, for it is found that on the complete removal of the mercury many of the inactive organisms recover; in practice its action is therefore partly disinfectant and partly antiseptic. The symptoms of mercuric poisoning and the general action have been discussed under the chapter on mercury.

Mercuric chloride solution (1 in 2,000 to 4,000) is used extensively in

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surgery to disinfect the hands, skin, and wounds, but is very irritant even to the unbroken skin and must not be applied to more delicate tissues. It corrodes steel and this precludes its use to protect instruments before use. It is sometimes employed in the form of a soap and to impregnate bandages, cottonwool, gauze, catgut, etc., but it renders all of these irritant and corrosive so that they should not be applied directly to wounded surfaces. It differs from the carbolic acid group in preserving its disinfectant powers in oils and fatty vehicles, in which it is only slightly soluble and which it therefore leaves readily for the fluids of the microbes. It also differs from carbolic acid in the fact that the presence of sodium chloride reduces its disinfectant action because it lessens the amount of the free Hg ion. The disinfectant action of corrosive sublimate is much diminished by the presence of protein and it has less penetrating power than carbolic acid. Mercuric chloride dissolved in 25 per cent alcohol is more active as a disinfectant than when in water probably due to the fact that the dilute alcohol may favor the penetration of the poison. To utilize this fact it is often used in the form of **Harrington's Solution** which consists of 640 cc. of 95 per cent alcohol, 60 cc. of hydrochloric acid, 300 cc. of water and 0.8 gram of bichloride of mercury. On the other hand, mercuric chloride loses its disinfectant power in 95 per cent alcohol because it is not dissociated in the alcohol and as is well known the free ion is necessary for the disinfectant property. It precipitates protein like other metallic salts and has a further specific toxic action on living tissue.

Various other mercurial salts have been suggested as disinfectants, for example the cyanide, the periodide and potassium mercuric iodide. The latter is a complex salt formed by the interaction of one molecule of HgI_2 with two molecules of KI. An excess of potassium iodide prevents the precipitation of mercuric iodide on standing. Several proprietary preparations of potassium mercuric iodide with the addition of ammonium chloride or sodium bicarbonate and a dye are available in the form of tablets for the preparation of antiseptic solutions in surgery.

The yellow oxide of mercury is insoluble. It is used in the form of an ointment for application to the eye. Preparations containing in addition small amounts of epinephrine, menthol and phenol are also available for the same purpose.

Preparations

U. S. P.

Hydrargyri Bichloridum, mercury bichloride, a heavy crystalline white powder.

Toxitabellæ Hydrargyri Bichloridi Magnæ. Each large tablet of the bichloride of mercury contains 0.5 gram of corrosive chloride of mercury. They are colored and are of an irregular shape in order to distinguish them from tablets which are intended for internal administration, these tablets being used only for the preparation of disinfectant solutions. They form a solution of the strength of 1 to 2000 when one tablet is added to a liter of water.

Toxitabellæ Hydrargyri Bichloridi Parvæ. Small tablets of mercury bichloride contain on an average 0.125 gram of the bichloride of mercury. These tablets must be colored and of an irregular shape.

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B. P.

HYDRARGYRI PERCHLORIDUM, corrosive sublimate. Dose, 0.002 to 0.004 gram.

LIQUOR HYDRARGYRI PERCHLORIDI. The solution of mercuric chloride contains 0.1 gram of mercuric chloride to 100 cc. of water; 4 mil. contain 0.004 gram of mercuric chloride. Dose, 2 to 4 mil. (30 to 60 min.)

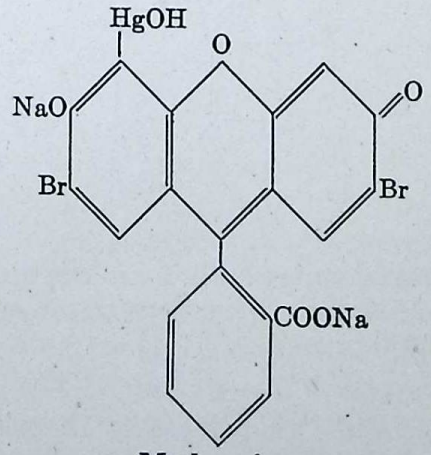
PHENYLHYDRARGYRI NITRAS, phenylmercuric nitrate, a white crystalline powder, slightly soluble in water.

7. Organic Mercurials

In order to reduce the toxic and caustic properties of inorganic mercury compounds, and still retain the antiseptic action of this metal, a number of organic derivatives containing mercury have been introduced into medical practice. These have been widely used as antiseptics. They are usually available in the form of aqueous solutions, tinctures and ointments.

The first of these compounds used as an antiseptic was **phenylmercuric chloride** but because of its insolubility this was supplanted by the more soluble basic **phenylmercuric nitrate** (merphenyl nitrate). The latter is a molecular compound of phenylmercuric nitrate and hydroxide—$C_6H_5HgNO_3.C_6H_5HgOH$. Other phenylmercuric compounds used as antiseptics are phenylmercuric (merphenyl), borate and phenylmercuric (merphenyl) picrate. These are used as tinctures for application to the skin.

Merbromin or **mercurochrome** was originally introduced for intravenous as well as local use. It is the disodium salt of 2,7-dibrom-4 hydroxymercurifluorescein. It is only moderately active as an antiseptic but is



Merbromin

non-irritating and when applied to the skin, mucous membranes or wounds exerts bacteriostatic and bactericidal action. It is slower acting than the tincture of iodine but has a more prolonged bacteriostatic action than the latter. It is used either as a 2 per cent aqueous solution or in an aqueous alcohol-acetone solution (surgical solution of merbromin). The latter is used for preoperative skin disinfection.

A 1 per cent aqueous solution of merbromin may be applied to the mucosa of the bladder, renal pelvis and urethra. It should not be ad-

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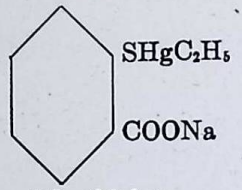
ministered intravenously as this may be followed by severe toxic symptoms.

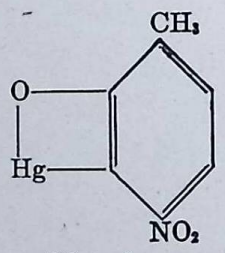
Merthiolate, the sodium salt of ethyl mercurithiosalicylate, is germicidal for many non-sporulating bacteria and is also fungicidal, but like the other organic mercurials available cannot always achieve sterilization especially if spore-forming organisms are present.



Merthiolate

In addition to its use as a local antiseptic and disinfectant, merthiolate is used in a concentration of 1 : 10,000 as a preservative of biologicals. For application to the denuded skin or wounds and for the disinfection of instruments a 1 : 1,000 aqueous solution is recommended. For application to mucous membranes more dilute aqueous solutions are used: in the eye, 1:5,000 to 10,000; nose, 1:2,000 to 5,000; urethra, 1:5,000 to 30,000.

Metaphen, the anhydride of 4-nitro-3-hydroxy-mercuri-*ortho* cresol is a relatively non-toxic, non-irritating antiseptic. Aqueous solutions of the drug are prepared with the aid of sodium hydroxide which opens the anhydride ring with the formation of the sodium derivative.



Metaphen

For disinfection of instruments and for application to the skin a solution of 1:1,000 to 5,000; for irrigations of the eye or urethra, a solution of 1:5,000 to 10,000 is used.

8. Silver and Other Metallic Disinfectants

The salts of several other metals have been used as disinfectants and antiseptics. Silver nitrate is the most important of these and plays a large rôle in the treatment of infections of the mucous membranes, especially that of the eye. This disinfectant action is accompanied by intense irritation, but silver nitrate has very slight powers of penetration because it is rendered insoluble and therefore inactive by the chlorides of the tissues. Silver nitrate is used in solutions of 1 to 2 per cent as a disinfectant in infectious ophthalmia, or in more dilute form (1 in 200 to 400) for more frequent application. It has also been used as

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an injection in gonorrheal infection of the urethra in the strength of 1 in 500 to 2,000, and in various other conditions. General poisoning is unknown from this use of silver, but its intensely caustic action and the limited extent to which it penetrates have prevented its wider employment. This irritant action of the nitrate has led to the introduction of various organic compounds (see Silver, p. 131), which are less dissociated in solution and thus are less corrosive. But these lose their disinfectant power in the same ratio as they become less irritant, for the tissue destruction arises from the same factor as the disinfectant action, the free silver ion. The effects of silver after absorption have been discussed, but it may be mentioned again that long continued use of any silver preparation even locally may produce **argyria**, in which the skin assumes a metallic dusky discoloration due to the deposition of the metal in the epidermis.

Colloidal silver preparations are used where it is desired to avoid the irritation, pain, astringency and corrosive action of silver nitrate. These consist of variable mixtures of metallic silver, silver oxide, and silver protein complexes in colloidal form. On solution in water a colloidal solution is formed in which so few free silver ions are present that chlorides or proteins are not precipitated.

The available preparations of colloidal silver are of five general types: (1) protein silver, strong type, (2) protein silver, mild type, (3) collargol type, (4) electric type and (5) silver halides. Protargol is an example of protein silver, strong type. This group manifests the strongest germicidal action but is mildly irritant. Protein silver, mild type, contains two to three times as much silver as the strong type but is less irritant than the latter. Among the proprietary preparations of this group are argyn, cargentos, silvol and solargentum. The collargol type contains about 78 per cent of metallic silver reduced to colloidal form and stabilized with denatured proteins. The silver halides consist of mixtures of silver halide salts with suitable diluents. Unlike the other colloidal silver solutions which are brown, these are colorless. Lunasol and neosilvol are typical proprietary preparations of this group.

The above described colloidal silver compounds are used principally as mild antiseptics on mucous membranes. The strong protein silver group is used in concentrations varying from 0.1 to 10 per cent; the mild protein silver in 5 to 50 per cent and collargol in 0.02 to 1 per cent solution.

Among other silver salts used as antiseptics may be mentioned silver lactate and silver picrate. The introduction of the sulfonamide and antibiotic drugs has largely displaced these as well as other silver preparations from their former importance.

Among the other metallic compounds used as antiseptics may be mentioned basic bismuth subnitrate which is used in the form of "**surgical bismuth paste**" comprised of 1 part of $BiNO_3$ in 2 parts of yellow petrolatum. Bismuth tribromphenate (**xeroform**), a basic bismuth salt of tribromphenol of variable composition is used as a powder, lotion or ointment for external application.

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PREPARATIONS

U. S. P.

ARGENTUM PROTEINICUM FORTE, strong protein silver, contains about 8 per cent of silver. It is a brown, odorless powder. Solutions should be freshly prepared and kept in amber-colored bottles.

ARGENTUM PROTEINICUM MITE, mild protein silver, contains about 20 per cent of silver.

B. P.

ARGENTOPROTEINUM, silver protein, contains about 8 per cent of silver.

9. Oxidizing Disinfectants

Peroxide of Hydrogen.—Hydrogen peroxide or dioxide (H_2O_2) tends to break down into water and oxygen very rapidly in the presence of many substances, which in themselves may be either oxidizing or reducing. Among the bodies which induce this decomposition are the peroxidase ferments, which are found in all forms of living matter, and the peroxide of hydrogen is therefore decomposed when brought in contact with the tissues; the oxygen thus liberated tends to oxidize its surroundings and its chief effects are therefore due to its oxidizing properties. It is generally met with in dilute solution in water, and in this form alone is used in medicine. A concentrated solution corrodes the skin, leaving a white eschar. Brought in contact with the skin, peroxide of hydrogen solution is decomposed, and numerous bubbles of oxygen are formed, but this decomposition proceeds much more rapidly when it is applied to denuded surfaces or to mucous membranes. The oxygen is formed in such quantity that some irritation may follow, and thus dogs often vomit when it is administered in quantity by the mouth. When it is injected subcutaneously, a large amount of oxygen is formed in the subcutaneous tissue, but some of the peroxide escapes decomposition and is absorbed into the blood. Here the decomposition proceeds more violently, the red blood cells having a strong catalytic action, and the oxygen set free may cause emboli and lead to sudden death. The formation of emboli is seen most frequently in the rabbit, but was in all probability the cause of death in one case of fatal poisoning in man, in which a solution of hydrogen peroxide had been used to wash out the pleural cavity. Hemiplegia has been observed following its use for this purpose, apparently from embolism of the cerebral arteries. Emboli are not formed in the dog on hypodermic injection, nor in either dogs or rabbits poisoned by the stomach—in the latter case probably because the liquid is more slowly absorbed and is almost entirely decomposed in the mucous membrane. Even in the blood and tissues the whole of the peroxide is not decomposed, for several observers have found traces of it excreted in the urine.

The catalysis of hydrogen peroxide occurs in the lower forms of life as well as in the higher. Thus germinating seeds, yeast, infusoria and the microbes all free oxygen from the solution, and in fact, a rough estimate of the number of microbes in water may be formed from the amount of oxygen given off by it on the addition of the peroxide (Gottstein). This decomposition is fatal to most of these lower forms, from

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the nascent oxygen, and peroxide of hydrogen is therefore a powerful disinfectant in water, a 3 per cent solution proving as strongly bactericidal as a 1 per mille solution of corrosive sublimate; but when the microbes are contained in a medium with much organic substance, as in wounds, the bactericidal action is very much reduced. This appears to be due to the too rapid decomposition of the peroxide, which escapes as bubbles of oxygen, comparatively little oxidation taking place. This may be exemplified by its action on the blood; when normal blood in a test-tube is treated with peroxide, it froths up and the oxygen escapes, leaving the blood unaltered. If, however, some hydrocyanic acid has been added to the blood some time previously so as to weaken the ferment, there is little or no effervescence and the hemoglobin is changed to methemoglobin by the peroxide remaining and freeing its oxygen more slowly. The peroxide therefore oxidizes most powerfully when it is slowly decomposed, while the rapid action of the ferments tends to dissipate the oxygen in the molecular form which has comparatively slight oxidizing and disinfectant powers.

Other peroxides used in medicine are sodium peroxide (Na_2O_2) which is applied as a paste in acne or as a soap to remove comedones, and zinc peroxide (ZnO_2) used in the form of a cream for application to wounds. Aqueous suspensions of ZnO_2, activated by heating, are particularly useful in infections caused by micro-aerophilic or anerobic organisms.

Therapeutic Uses.—Hydrogen peroxide is used locally as a disinfectant. In pus cavities the oxygen is freed with great rapidity. Peroxide solutions differ from most other disinfectants in the short duration of the action, which passes off as soon as all the oxygen is liberated. In addition to its microbicidal action proper, this agent loosens and destroys masses of infected material by the mechanical effect of the liberation of the gas, and the wound or cavity is thus cleaned by it more perfectly than by washing with ordinary disinfectant solutions. Most surgeons believe that this mechanical action is of more importance than the direct germicidal effect. The solution has been recommended for use in ophthalmic practice, and for this purpose may be diluted one half.

Peroxide has been used to destroy the bacteria of drinking water and 10 to 15 cc. of the pharmacopeial solution is found to reduce the bacteria in a liter of water more than one hundred times; about twice as much is required to have the same effect in milk.

Preparations

Liquor Hydrogenii Peroxidi (U. S. P., B. P.), solution of hydrogen peroxide, an aqueous solution containing about 3 per cent of H_2O_2.

Liquor Hydrogenii Peroxidi Fortior (U. S. P.), stronger solution of hydrogen peroxide, contains about 8 per cent of H_2O_2.

Zinci Peroxidum Medicinale (U. S. P.), medicinal zinc peroxide, a mixture of zinc peroxide, zinc oxide and zinc hydroxide.

Other Oxidizing Disinfectants.—Some older disinfectants also owe their powers to liberated oxygen, and among these that most largely employed is the *Permanganate of Potassium.*

When a solution of this salt comes in contact with organic matter,

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such as albumin, the permanganate at once parts with some of its oxygen, which attaches itself to the albumin. Permanganate is thus poisonous to protoplasm, not through the presence of the whole molecule, but in consequence of the oxidation of the proteins. As soon as the permanganate is reduced, it of course loses this action, so that the oxidizing effect is limited to the skin and the surface of the mucous membranes. Concentrated solutions irritate and even corrode the skin, and induce gastro-enteritis when swallowed. Permanganate solutions are disinfectants of considerable power, owing to their oxidizing bacteria and thus destroying them. They fail to penetrate deeply in an active form, and this renders them of less value than many other disinfectants, except in very superficial infection.

Therapeutic Uses.—Permanganate is used for its disinfectant and deodorant action, as an application to gangrenous ulcers and cancerous sores. In dilute solution it may be used as a gargle and mouth wash ($\frac{1}{4}$ per cent), to disinfect the hands (1 per cent), which it stains brown, and for other similar purposes. It was formerly widely used for irrigation of the urethra in gonorrhea. The stain on the skin may be removed by lemon juice or vinegar.

It has been recommended in poisoning with phosphorus, prussic acid, morphine and other alkaloids, on the theory that these poisons are oxidized by it in the stomach, and thus rendered harmless. But permanganate also oxidizes the gastric mucous membrane, and it has not been shown that it attacks morphine in preference to the proteins; the treatment is certainly less reliable than the use of the stomach tube; permanganate has of course no action on morphine after absorption. In snake-bite, permanganate has been used to wash the wound and also to inject around it; it has no effect upon the poison already absorbed.

Potassium permanganate has proved to be of value in the dermatitis due to poison ivy. For this purpose it is used in rather strong concentrations, 1 per cent solutions sometimes being effective where weaker strengths have failed to give relief. The best results are obtained by first applying a 3 per cent solution of sodium bicarbonate to the affected area and after this has dried applying the permanganate solution.

Condy's Fluid is a strong solution of impure permanganate, which is used to disinfect and deodorize urinals and feces, but must be poured on them, and cannot be employed to disinfect rooms.

Preparation

Potassii Permanganas (U. S. P., B. P.) ($KMnO_4$) forms slender crystals of a dark purple color and a sweetish, afterward disagreeable and astringent taste, soluble in 16 parts of water, reduced by alcohol and other organic bodies. Dose B. P., 0.06 to 0.2 gram.

10. Boracic Acid and Borax

Boracic or boric acid ($B(OH)_3$) is a very weak acid, and it is doubtful whether the hydrogen ions or acidity play any part in its action, or whether the whole is not to be referred to the rest of the molecule. The ordinary sodium compound, borax, $Na_2B_4O_7$, is stated by some

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authors to be equally active, but is alkaline in reaction, so that the exact relative importance of the two ions of boric acid cannot be determined. Boracic acid and its sodium salt have some antiseptic power, for in 2½ per cent solution almost all forms of bacilli stop growing; but they are not destroyed, even the delicate anthrax bacilli being found capable of further growth after exposure to a 4 per cent solution for twenty-four hours. Boracic acid is therefore valueless as a disinfectant, but has been used as an antiseptic dressing; it has the advantage over many other antiseptics of inducing very little irritation and of being only slightly poisonous, but experience has shown that it cannot be used with impunity in very large quantities.

Toxicity.—Boracic acid and borax are only feebly toxic, but large quantities taken by the mouth cause gastric and intestinal irritation, as is evidenced by vomiting and purging, and even smaller amounts are said to act as mild aperients in some cases. Not infrequently repeated small doses of boric acid have induced albuminuria, especially in persons predisposed to it.

Boracic acid has been widely used as an antiseptic dressing and also internally, and a number of cases of serious poisoning have been recorded from its absorption. The symptoms arose in part from the alimentary canal: uneasiness in the abdomen, vomiting, diarrhea, dryness of the throat, and difficulty in swallowing; sleeplessness, great muscular weakness and depression, dimness of sight and headache were also complained of, and in severe cases collapse and death followed. The prolonged use of boric acid, internally or externally, has repeatedly led to falling of the hair, eczema, and psoriasis. Papular eruptions are common in cases of poisoning and local edemas and swelling of the skin sometimes appear. A gray line on the gums, similar to that seen in lead poisoning, is stated to occur, along with irritation of the mouth. Chemical examination of the organs in cases of fatal poisoning has shown that the largest amount of boracic acid is stored in the brain, which in turn is followed closely by the liver.

Boracic acid and borax are excreted in the urine, in which they appear within a few minutes after ingestion; over half the quantity taken is excreted within twelve hours, but afterwards the elimination proceeds more slowly, so that traces may be found in the urine for five days or more; the urine becomes alkaline after sufficient amounts of borax, as after any other alkaline preparation.

Therapeutic Use.—Boracic acid has been used as a surgical antiseptic in solution (4 per cent), ointment, or on lint, and the solution of the acid or of borax is also used as a wash in aphthæ and other forms of irritation of the mouth. Boracic acid solution is frequently used in ophthalmic surgery, as being less irritant to the eye than the more powerful antiseptics. Boracic acid and borax have also in the past been added to milk or other food as preservatives but modern methods of food conservation no longer countenance such adulteration.

Poisoning with boric acid, often with fatal consequences, has followed the use of boric acid powder in wounds, the application of the ointment to the denuded skin, the solution into the body cavities, and accidental

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administration of the drug by injection or in infants' food. In view of its relatively feeble antiseptic properties and the availability of more potent antiseptics it probably deserves to be relegated to the limbo of outmoded remedies.

PREPARATIONS

U. S. P.

ACIDUM BORICUM, boric acid, colorless crystals with a faintly bitter taste soluble to about 5 per cent in water or in alcohol, and to about 25 per cent in glycerin.

GLYCERITUM BOROGLYCERINI, contains 31 per cent of boric acid in glycerin.

UNGUENTUM ACIDI BORICI, ointment of boric acid, contains 10 per cent of boric acid.

SODII BORAS, sodium borate or borax, contains about 54 per cent of $Na_2B_4O_7$, corresponding to not less than 99 per cent of the crystallized salt (12 gr.).

B. P.

ACIDUM BORICUM, boric or boracic acid (H_3BO_3). Dose, 0.3 to 1 gram.

GLYCERINUM ACIDI BORICI, contains about 30 per cent of boric acid in glycerin. Dose, 0.6 to 2 mil.

UNGUENTUM ACIDI BORICI, contains 10 per cent boric acid in paraffin ointment.

BORAX, sodium borate, colorless crystals with a sweetish alkaline taste. Soluble in water to the extent of about 6 per cent giving the water an alkaline reaction. Dose, 0.3 to 1 gram.

GLYCERINUM BORACIS, contains 12 per cent of borax in glycerin. Dose, 2 to 4 mil.

MEL BORACIS, contains 10 per cent of borax in honey and glycerin.

11. Potassium Chlorate

The chlorate of potassium introduced into therapeutics on the erroneous theory that it would supply oxygen to the tissues, has been used very extensively for its effects in certain diseases of the mouth. It was supposed to be entirely devoid of poisonous properties, but may give rise to very grave and even fatal symptoms in some instances. But the conditions which determine their appearance are not universally present, for very often large quantities have been taken with impunity.

Symptoms.—The chlorates have a cool, saline taste, which persists for a long time owing to their being excreted in part in the saliva. Concentrated solutions may cause nausea and vomiting from their local salt-action in the stomach, and their absorption is often followed by considerable diuresis from a similar action in the kidney. In the great majority of cases no further effects are observed.

In some individuals, however, symptoms arise from a single large dose, or from smaller quantities taken repeatedly. In **Acute Chlorate Poisoning**, the first symptom is often prolonged and violent vomiting, with pain in the stomach region; diarrhea and a dark cyanotic color of the skin and mucous membranes follow, the respiration is at first dyspneic and then weak, the pulse quick and feeble, sometimes irregular. The patient complains of headache, giddiness and muscular weakness, is restless, and eventually becomes comatose before death.

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In **Subacute Poisoning,** vomiting and diarrhea are also observed, and the vomited matter often contains large quantities of bile, less often blood. There may be complete anuria for some time, or the urine is scanty and at first dark colored, then deep reddish-brown; it contains hemoglobin, methemoglobin, and hematin in solution. On standing, it deposits casts of brown amorphous particles, which arise from the destruction of the red cells of the blood, and chlorates are contained in it in considerable quantity. The methemoglobin may disappear from the urine after one or two days, but the casts remain longer. The skin is often icteric in color, and in some cases erythematous eruptions have been observed. Headache, muscular weakness and abdominal pain are complained of, and uremic symptoms may arise—delirium and convulsions, or confusion and coma. Death has followed from these last as late as a week after the first symptoms of poisoning were observed, but in several cases complete recovery has followed even the gravest symptoms.

The view that the blood changes, and especially the formation of methemoglobin, are responsible for the symptoms seen in chlorate poisoning, has been called in question. Potassium chlorate administered to animals so as to produce either acute or subacute poisoning is said to produce methemoglobin in only a small percentage of the cases. In some instances it will appear in the blood postmortem and it forms more often when death is delayed for some hours. Frequently it only appears very late, even when the animals are moribund. In case of death the kidney activity previous to death is more or less completely inhibited while survival is dependent upon immediate and continued diuresis.

Sodium chlorate seems more prone to produce methemoglobin *in vivo* than does potassium chlorate, while such formation does not occur when magnesium or calcium chlorate is administered. *In vitro* the action is just the reverse, the magnesium and calcium salts being more active than either the sodium or the potassium salt.

Chlorate has little or no direct effect on the central nervous system or the circulation, though these are secondarily affected by the asphyxia and renal changes.

Very little chlorate is reduced in the blood and tissues, for 90 to 96 per cent of the amount administered has been recovered from the urine. Small quantities appear also in the saliva and in other secretions, such as the perspiration, milk, tears, and nasal mucus, and some has been found to pass from the mother to the fetus *in utero*.

Chlorates hardly retard the growth of bacteria in cultures more than other indifferent salts, and no adequate explanation has been offered for their use in infections of the mouth and throat.

The **Bromates** and **Iodates** have been less often the subject of investigation than the chlorates, and are not used in therapeutics. The iodates are more poisonous than the bromates and these again than the chlorates; the iodates destroy the red cells more rapidly but form less methemoglobin than the chlorates in test-tube experiments. Iodates induce fatty degeneration of the liver and congestion and extravasation in the alimentary tract. Some iodide is formed from them in the body.

The action of the **Perchlorates** has been examined by Kerry and Rost. In the frog the perchlorate of sodium ($NaClO_4$) induces fibrillary twitching and clonic contractions of the muscles; the muscle curve is prolonged in the same way as by veratrine, and rigor eventually follows as in caffeine poisoning. The reflex excitability is increased and the heart is slow and irregular. The effects of the perchlorate on mammals differ considerably in different species; in the rat, mouse, and guinea-pig the reflex excitability is enormously increased and

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tetanic convulsions may arise from this action; in the cat a certain stiffness, muscular paresis and tremor can be made out after the injection of large quantities of perchlorate, but these animals as well as the rabbit and dog are not easily killed by it.

Therapeutic Uses.—The chlorate of potassium is used chiefly as a mouth wash and gargle in irritated conditions of the mouth and throat, such as aphthæ, and in the tenderness and ulceration of the gums and mouth induced by the prolonged use of mercury. It may also be given as a prophylactic to lessen stomatitis when mercury is being prescribed. In catarrh of the throat it is often used with apparently good effects.

It is used in 2 to 4 per cent solution. In children a somewhat stronger solution with syrup or honey may be used to brush out the mouth, but care should be taken that none is swallowed. The local action of the chlorates has not been explained, and it may be due to the salt-action in part, though not wholly and it is not impossible that equally satisfactory results might be obtained by the use of the chlorides or nitrates.

Poisoning.—The fatal dose of chlorate varies extremely, as little as 1 gram having proved fatal in a child, while 40 to 50 grams have been swallowed by adults without marked symptoms. Chlorate poisoning is now very rare; it is said to be more liable to occur in nephritics than in normal persons. As a general rule symptoms appear only two to three hours after the drug has been taken, and the treatment is purely symptomatic—central nervous stimulants, ice for vomiting, etc.; alkalies may be given and diuretics and large amounts of fluid to flush out the kidneys.

PREPARATIONS

B. P.

POTASSII CHLORAS, potassium chlorate, colorless prismatic crystals with a saline taste. The dry salts form explosive mixtures with organic or other reducing substances, and such mixtures are therefore to be kept cool, and ought not to be ground together, as heat and pressure are liable to cause explosions. Dose, 0.3 to 0.6 gram.

TABELLÆ POTASSII CHLORATIS, tablets of potassium chlorate. Dose, 0.3 to 0.6 gram.

12. Iodine

Iodine is widely used to disinfect the skin before operation, as it is found to penetrate readily into the pores and has a powerful germicidal action. Its irritant effects preclude its more general use. It is generally employed in the strength of $2\frac{1}{2}$ to 5 per cent in 10 per cent potassium iodide solution or in alcohol, and is painted on the site of operation a few minutes before the incision is made.

A solution which is recommended as being relatively non-irritant and yet efficient as a germicide, contains 2 per cent of iodine and 2.4 per cent potassium iodide in 50 per cent ethyl alcohol.

PREPARATIONS

U. S. P.

TINCTURA IODI. Tincture of iodine contains 7 per cent of iodine and 5 per cent of potassium iodide in about 85 per cent alcohol.

TINCTURA IODI MITIS. The mild tincture of iodine contains 2 per cent of iodine and 2.3 per cent of sodium iodide in diluted alcohol.

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B. P.

LIQUOR IODI FORTIS. The strong tincture or solution of iodine contains 10 per cent of iodine and 6 per cent of potassium iodide in approximately 80 per cent alcohol.

LIQUOR IODI MITIS. The weak solution or tincture contains 2.5 per cent of iodine and 1.5 per cent of potassium iodide in approximately 85 per cent alcohol.

LIQUOR IODI SIMPLEX. The simple solution of iodine contains 9 per cent of iodine in 95 per cent alcohol.

13. Iodoform

A number of iodine compounds have been introduced into therapeutics as applications to wounded surfaces. The most widely known of these is Iodoform (CHI_3), which corresponds in its chemical structure to chloroform, and was formerly used very extensively in surgery and gave rise to poisoning repeatedly. It has gradually fallen into disrepute and is little used today.

Iodoform has no marked **Local Action** on the skin or mucous membranes. Some persons have a special idiosyncrasy for it which betrays itself in an eruption developed in the skin near where iodoform has been applied. It seems to have some anesthetic action when applied in large quantity to wounded surfaces.

Toxicology.—The symptoms of iodoform intoxication in man generally set in with anxiety, general depression and discomfort. The patient becomes sleepless and restless, complains of giddiness and headache and often of the taste and odor of iodoform in the mouth and nose. The pulse is generally greatly accelerated, and a rise of temperature is said to have occurred in some cases in which no septic poisoning could be found to account for it. The depression deepens into true melancholia accompanied by hallucinations, the patient often suffering from the delusion of persecution, which may induce him to attempt suicide. As a general rule this melancholia is followed by attacks of violent delirium and mania, lasting for hours or days, and in fatal cases, by collapse and death. In other cases the condition has passed into permanent insanity and dementia. A rarer result of the absorption of iodoform is deep sleep passing into stupor and collapse without any symptoms of cerebral excitement.

In milder cases of poisoning the patient suffers only from the unpleasant taste and odor, from headache and not infrequently from nausea and vomiting.

In the dog and cat iodoform generally causes deep sleep and stupor, with lessened excitability of the spinal cord and of the motor areas of the brain; but after large doses excitement and convulsions of clonic and tonic types have been observed. In the frog it paralyzes the central nervous system and the heart without eliciting any symptoms of excitement. No narcosis is observed in the rabbit even after fatal doses. After prolonged administration albuminuria is often observed in animals, and the iodine of the thyroid has been found to be increased by iodoform, as by other bodies which free iodine in the tissues.

After fatal iodoform poisoning in man and animals, the liver, kidney, heart, and muscles are generally found to have undergone fatty degeneration. In addition, irritation of the gastric and intestinal mucous mem-

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brane has been observed, and the epithelial cells are often degenerated. Ecchymoses occur beneath the endocardium, in the kidney, and elsewhere; and congestion of the meninges is described.

Absorption and Excretion.—Iodoform is readily decomposed in the presence of alkaline fluids and in protein solutions, and some decomposition undoubtedly takes place in wounds; the iodine liberated combines with the alkalies of the fluids to form iodides, for these have been shown to be present, and iodalbuminates are presumably formed in the same way as by free iodine. Some of the iodoform is perhaps absorbed unchanged. After iodoform absorption, iodine has been shown to be present in the saliva, perspiration, and bronchial secretion, as after the ingestion of iodine or iodides; but it is chiefly excreted in the urine in the form of iodides and partly in organic combination. The tissues apparently retain it very tenaciously, for iodides have been found in the urine for more than a month after the administration of iodoform.

Iodol or tetraiodopyrrol (C_4I_4NH), which has no odor or taste, is insoluble in water, but is absorbed from mucous surfaces and from wounds. It is decomposed in the tissues, and leads to the excretion of iodides in the urine, and in very large doses gives rise to symptoms in animals resembling those produced by iodoform. **Iocamfen** is a liquid mixture of iodine, phenol and camphor. It combines the antiseptic properties of iodine with the analgesic and stimulating effects of phenol and camphor.

Dusting Powders containing iodine have also been recommended as substitutes for iodoform for the application to wounds, abscess cavities, granulating surfaces, etc. They avoid the odor of iodoform and are less toxic but also lack its activity. What value they possess is probably due to their acting as absorbent powders. Among these preparations may be mentioned the iodine derivatives of thymol (aristol); of quinoline (loretin and vioform); of phenolphthalein (nosophen, antinosine, eudoxine); and of cresol (losophan, europhen).

Therapeutic Uses.—Iodoform has been chiefly employed in surgical treatment as an application to wounds, skin diseases, burns, granulating surfaces with a profuse secretion, and in slowly healing abscess cavities. It may be applied as a dusting powder, as an ointment, or in gauze or bandages saturated with it. It has been shown that it has very weak antiseptic properties, and many surgeons take the precaution of disinfecting the powder before applying it, and use it for its effect on the tissues of the wound and not for its effects on the germs. Applied in ordinary quantity to small surfaces it seems to be a perfectly safe remedy, cases of poisoning occurring only when large cavities are treated with it, or when it is applied to very large absorbing surfaces.

Preparations

U. S. P.

Thymolis Iodidum, thymol iodide, aristol ($(C_6H_2.CH_3.C_3H_7.OI)_2$, a yellowish brown powder; tasteless, odorless, insoluble in water and containing not less than 43 per cent of iodine.

B. P.

Iodoformum, iodoform, small, lemon-colored crystals, possessing a very penetrating, persistent, and disagreeable odor and taste, practically insoluble in water, soluble in alcohol, ether, fixed oils, glycerin, etc. Dose, 0.03 to 0.2 gram.

Oculentum Iodoformi. The iodoform ointment for the eye contains 4 per cent of iodoform.

Suppositorium Iodoformi. Each suppository contains 0.2 gram of iodoform.

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14. Chlorine Preparations

The disinfectant action of many organic substances is intensified when chlorine is substituted for hydrogen; for example, chlorphenol is more powerful than carbolic acid. This is not owing to chlorine being freed from the molecule, but from the same chemical property which renders trichloracetic acid a more readily dissociated and therefore stronger acid than acetic acid.

But several chlorine compounds have been introduced as disinfectants which owe their value to the chlorine liberated by them. Chlorine itself is a powerful poison to all living matter, including the bacteria, and has been used for the disinfection of water and inanimate objects. It cannot be employed in surgery, owing to its intense irritant action, and volatility. Compounds which give off chlorine more slowly than the solution have therefore been introduced; solutions of sodium hypochlorite have been largely employed to irrigate septic wounds (*Eusol* or *Dakin's solution*) and have proved highly efficient as disinfectants.

Dakin's solution is prepared by adding chlorinated lime to a solution of sodium carbonate and after filtration of this solution boric acid is added. The solution, which is nearly neutral, should contain between 0.45 and 0.5 per cent of sodium hypochlorite. *Eusol*, made by adding boric acid to a solution of chlorinated lime, contains the equivalent of 0.27 per cent of hypochlorous acid.

As the chlorine escapes the fluid becomes slightly alkaline but it is not strongly irritant. It penetrates well as it does not precipitate proteins, and it dissolves necrotic tissue and pus to some extent.

A firmer combination is met with in the *chloramines*, in which the chlorine is attached to the nitrogen of an organic molecule. The best known of these is the chloramine-T (*Chloramina*) of Dakin, a toluene derivative of the formula, $(CH_3)C_6H_4SO_2NNaCl$, containing about 12.5 per cent of active chlorine. This chloramine is a white crystalline substance smelling faintly of chlorine, and is used in 1 to 2 per cent solution in water for the same purposes as hypochlorite solution, especially on wounds as an irrigating fluid and as a mouth wash. It is more stable than the hypochlorite, does not dissolve necrotic tissue in the same way, nor become alkaline, nor does it give up its chlorine so rapidly; it is less irritant to the skin surrounding the wound.

Dichloramine-T, Paratoluene-sulphondichloramide, contains from 28 to 30 per cent of active chlorine. The yellowish powder is almost insoluble in water but is soluble in eucalyptol and in chlorinated paraffin. It is an active germicide possessing a gradual sustained action. It is more irritant than chloramine and also more solvent.

Dichloramine dissolved in chlorinated paraffin may be used for nasopharyngeal work in a 1 to 2 per cent solution; on wounds a 5 per cent solution is used. Such solutions are not very stable and should not be kept for more than two or three days.

Chloroazodin or azochloramid is only slowly hydrolyzed and hence is claimed to have a more prolonged action than the Chloramines. It is used in a dilution of 1 : 3,000 dissolved in isotonic saline buffered at

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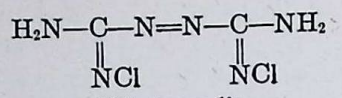
pH 7.4. For application to mucous membranes dilutions of 1 : 13,200 are used. It is also used as a constituent of dressings and packings for application to wounds and mucous membranes.



Chloroazodin

Hyclorite, a solution of chlorinated soda, sodium chloride and calcium hydroxide has seven times the available chlorine content of surgical solution of chlorinated soda. After proper dilution it is used like the latter.

Therapeutic Uses.—Hypochlorite solution, chloramine-T, dichloramine-T, and the other organic chlorine derivatives are used for the irrigation of infected wounds. They owe their activity entirely to the chlorine which they liberate and which is a general poison to all living matter, but if they are properly applied, the action on the microbes more than makes up for their tendency to damage the tissues of the host. On the other hand their use is necessarily limited to local infections.

PREPARATIONS

U. S. P.

LIQUOR SODII HYPOCHLORITIS, solution of sodium hypochlorite, contains about 5 per cent of NaOCl. It is not suitable for application to wounds but is diluted with water and made neutral with sodium bicarbonate forming the dilute solution of sodium hypochlorite. Labarraque's solution consists of a mixture of solution of sodium hypochlorite diluted with an equal volume of water.

CHLORAMINA–T. Chloramine–T is sodium paratoluenesulphonchloramide and contains about 12 per cent of active chlorine.

B. P.

LIQUOR SODÆ CHLORINATÆ CHIRURGICALIS. Dakin's solution. Contains between 0.5 and 0.55 per cent of available chlorine.

CHLORAMINA. Chloramine-T. Chloramine is sodium p-toluenesulphonchloramide.

15. The Antiseptic Dyes

The dyes which are used for their local antiseptic action belong to four classes of synthetic organic compounds: (1) the azo dyes; (2) the acridine dyes; (3) the fluorescein dyes, to which mercurochrome, which has already been considered, belongs; and (4) the triphenylmethane or rosaniline series.

Azo Dyes.—The Azo dyes contain the —N : N — linkage. Scarlet red or Scarlet R which is the oldest member of this group comprises toluylazotoluylazo betanaphthol (Biebrich or Scarlet red medicinal) and scarlet red sulfonate which is the sodium salt of azobenzene disulfonic acid. In addition to these, **dimazon** (diacetylamino-azotoluene) has similar actions and is used for the same purposes as the scarlet red compounds.

These compounds are claimed to have a stimulating effect on the proliferation of epithelial cells and hence are used to promote the growth of epithelium in the treatment of denuded areas of the skin. They are usually applied in the form of ointments. Dimazon is also available in the form of a dusting powder.

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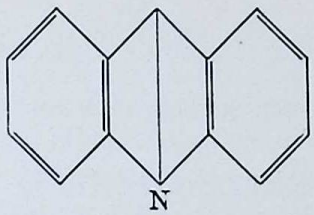
The Acridine Dyes—Acriflavine and Proflavine.—Acriflavine was introduced by Ehrlich in 1912 as having therapeutic properties in trypanosome infections. It was therefore called trypaflavine, but the name was later changed to acriflavine. It is a derivative of acridine, a coal-tar base, being diamino-methylacridinium chloride hydrochloride, while the base is often known as neutral acriflavine. Proflavin or proflavine sulfate differs from acriflavine in not possessing the methyl group attached to the nitrogen.



Acridine

These flavines or acridine dyes have been shown to possess considerable antiseptic and bactericidal properties, and on this account they have been introduced into medical and surgical practice as wound and surface disinfectants. They have a relatively low degree of toxicity and are comparatively free from local irritant properties. Acriflavine is apparently more active than proflavine, but it acts more slowly. Acriflavine base is particularly recommended where freedom from irritation is desirable, such as might be produced by the acid reactions of acriflavine hydrochloride or proflavine solutions.

Neutral acriflavine administered orally is eliminated in the urine. giving it a yellow fluorescence and exerting an antiseptic action in the urinary tract which begins in about two hours and may last eight hours. It is more marked in an alkaline urine, so that sodium bicarbonate is frequently given at the same time. Gastric distress may result if the use of the drug is prolonged.

A series of related acridine derivatives have been prepared and found to exert bactericidal effects sometimes superior to that of acriflavine and proflavine. Of these **9-aminoacridine** monohydrochloride is active against *Proteus* and certain *gram-positive* organisms. It has been used for irrigation of septic wounds.

Therapeutic Uses.—The acridine derivatives are used in a large variety of conditions in which an antiseptic or disinfectant is required, particularly in the case of organisms not susceptible to the sulfonamides. For wounds a strength of 1 to 1,000 is used in physiological salt solution, which may be applied by swabbing or as an irrigating fluid, and if desired the wound may be packed with gauze saturated with this solution. Evaporation should be prevented by the use of a protective dressing. Fresh wounds may be freely irrigated with the solution, and some being left in the wound, it may be closed and be permitted to heal.

In urethritis a dilute solution—1:4,000 or 6,000 may be used as an irrigating solution. In the throat or mouth a 1:1,000 solution may be used.

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For systemic effect acriflavine is administered orally in capsules or enteric coated tablets in doses of 0.2 gram daily. Prolonged administration may lead to renal and hepatic damage.

Solutions may be sterilized by boiling or by heating in an autoclave. They should be preserved in amber bottles, but solutions will not keep long, and those over a week old should be discarded.

PREPARATIONS

B. P.

ACRIFLAVINA, acriflavine; the hydrochlorides of diaminomethylacridinium chloride and diamino-acridine, a reddish crystalline powder. Dose, 0.03 to 0.1 gram.

PROFLAVINÆ SULPHAS, proflavine sulphate, proflavine, 2:8-diamino-acridine sulphate.

Triphenylmethane (Rosaniline) Derivatives.—The amino derivatives of triphenylmethane and its homologue, tolyldiphenylmethane, are designated as rosaniline and pararosaniline. The methyl derivatives of the latter constitute a series of basic dyes—**gentian violet, crystal violet, methyl violet** and **brilliant green**—which are effective germicides against gram-positive organisms. The gram-negative organisms, on the other hand, are highly resistant to these dyes.

These dyes are used for local application particularly to burns, ulcerated areas and weeping eczema.

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II. ANTISEPTICS USED CHIEFLY IN SKIN DISEASES

1. Pyrogallol

Pyrogallol, $C_6H_3(OH)_3$, was formerly widely used in the treatment of skin disorders but because of its toxicity when applied to large surfaces

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it has been discarded for safer and equally effective remedies. Pyrogallol produces nervous symptoms resembling those of carbolic acid, when given in very large doses to animals. In the cases of poisonings which have been observed in man, the symptoms arose almost exclusively from changes in the blood corpuscles. The red-blood cells become shrunken and angular and lose most of their hemoglobin, which escapes into the plasma and is changed into methemoglobin; the blood therefore assumes a chocolate-brown color, which may be detected in the living animal by the discoloration of the skin and mucous membranes. If the intoxication is not too acute, icterus follows, and hemoglobin and methemoglobin are excreted in the urine. In the blood, fragments of red cells and "shadows" or red cells deprived of their coloring matter, are seen in large numbers, and the spectrum of methemoglobin can be obtained easily. The kidneys are also affected, and the resulting nephritis is indicated by the presence in the urine of albumin, epithelium and casts, along with the products of the decomposition of the blood. The nephritis may lead to uremic convulsions, which are sometimes accompanied by the nervous tremors characteristic of this series, and also by dyspnea and cyanosis from the lack of hemoglobin in the blood. The formation of methemoglobin is due to the reducing properties of the drug. Pyrogallol is excreted in part in combination with sulfuric acid in the urine, in part as unknown oxidized products, which give the urine a dark brown or black color, even when no blood pigments are contained in it.

2. Chrysarobin

Chrysarobin is a mixture in varying proportions of neutral bodies which are closely related to the active principles of the anthracene purgatives. It is found in an impure form (Goa powder) in cavities in the Andira or Vouacapoua araroba, a tree growing in India and Brazil. Chrysarobin applied to the skin in a concentrated form, or in susceptible persons, causes itching, redness and swelling, less frequently papular or pustular eruptions; the skin and clothing are stained a reddish-brown color where it is applied. When swallowed, chrysarobin acts as a gastrointestinal irritant, causing vomiting and purging; some of it is absorbed, and in its excretion by the kidneys it causes nephritis in the rabbit with albumin and even blood in the urine. In man, slight albuminuria has been observed in some instances after its application to the skin; in animals, the epithelium of the renal tubules has been found to be necrosed, the glomeruli being less frequently affected. Part of that absorbed undergoes oxidation to chrysophanic acid in the body, but most of it passes through the tissues unchanged.

Therapeutic Uses.—Chrysarobin is used in skin diseases, especially in **psoriasis**, in which it is applied in ointment. In a strength of 10 to 20 per cent it has a keratolytic action while in more dilute form (5 per cent) it exercises a keratoplastic action. Because of its indirect parasiticidal activity it is used in the treatment of **ringworm**. It is also used in chronic eczema, hypertrophic lichen planus and other conditions in which there

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is thickening of the skin. Care must be taken in using chrysarobin to avoid irritation of the eyes.

Dioxyanthranol, a synthetic compound, is related to the active principle of chrysarobin. It is less irritant than chrysarobin and has been recommended as a substitute for it.

PREPARATIONS

CHRYSAROBINUM (U. S. P., B. P.), a substance obtained from Goa powder, which is found in the trunk of Andira araroba (Vouacapoua araroba, U. S. P.). It is a yellowish powder without odor or taste and is almost insoluble in water.

UNGUENTUM CHRYSAROBINI (U. S. P.), 6 per cent (B. P.), 4 per cent.

DITHRANOL (B. P.), dioxyanthranol, 1:8-dihydroxyanthranol, $C_{14}H_7(OH)_3$.

UNGUENTUM DITHRANOLIS (B. P.), ointment of dithranol, contains 0.1 per cent of dithranol in yellow soft paraffin.

3. Naphthol

The naphthols, $C_{10}H_7OH$, resemble carbolic acid in their antiseptic action but are much less soluble and less corrosive. Alpha-naphthol has been found to be more strongly antiseptic than the beta compound. Beta-naphthol is several times as strongly germicidal as carbolic acid, and is the form used in therapeutics.

The naphthols are irritating to the mucous membranes when they come in contact with them in solution or in vapor; thus they cause sneezing and coughing when applied to the respiratory passages, and in the course of excretion induce pain in the bladder and urethra with strangury and swelling of the mucous membrane. Large doses cause symptoms similar to those of carbolic acid poisoning, except that in the dog no convulsions have been observed, and in the other mammals they seem less pronounced. Injected subcutaneously or absorbed from the alimentary canal in animals, they induce active nephritis with the appearance of albumin and hemoglobin in the urine, and some nephritis has been caused in man from their external application. They seem to have less effect on the circulation and respiration than the other aromatic antiseptics, but resemble them in tending to destroy the red cells of the blood.

Occasionally naphthol has given rise to imperfect sight and partial retinal degeneration in man, and changes in the eye have been observed repeatedly in experiments on animals in which naphthol was absorbed. The retina is seen to be dotted over with bright points or to contain large yellow plaques. Atrophy of the optic nerve may follow, or subretinal effusion, and cataract has been developed in some experiments, from an inflammatory infiltration beginning in the ciliary body and iris and extending into the lens and finally into the posterior surface of the cornea.

The naphthols are excreted in the urine in combination with glycuronic and sulfuric acids, and these combinations and their oxidized products give the urine a reddish-brown color which may become deeper on exposure to the air.

Naphthalene, $C_{10}H_8$, the hydrocarbon from which naphthol is derived, is less soluble and does not give rise to acute symptoms in animals, but after prolonged treatment with it animals suffer from diarrhea and nephritis, with albumin and casts in the urine. The same changes in the retina are induced by naphthalene as by the naphthols. The antiseptic value of naphthalene is small, but it is oxidized to naphthols in the tissues and these acquire a toxic action. It is excreted in the urine as naphthol and further oxidation products, in combination with glycuronic and sulfuric acids.

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Therapeutic Uses.—Beta-naphthol was at first introduced as an external application in various forms of skin disease, in which it is used in ointment (5 to 10 per cent). It was formerly employed as an anthelmintic especially against hook-worm infections but has been replaced by safer and more effective drugs (*cf.* p. 757).

PREPARATIONS

BETANAPHTHOL (U. S. P., B. P.), NAPHTHOL. Beta-naphthol ($C_{10}H_7OH$), white or yellowish-white, insoluble crystals or powder, with a faint phenol odor and a hot taste. Dose, U. S. P., 0.12 gram; B. P., 0.3 to 0.6 gram.

ACETOMENAPHTHONUM (B. P.), acetomenaphthone, 1:4-diacetoxy-2-methylnaphthalene. Dose, 0.01 to 0.06 gram.

4. Resorcin

The three dioxybenzols—resorcin, pyrocatechin and hydroquinone—resemble carbolic acid in their effects, but produce a more intense stimulation of the central nervous system, for convulsions have been observed in man after their use. This is especially true for the last two, resorcin being much less toxic than these. Resorcin seems to be equally or more strongly antiseptic than phenol, and is somewhat less poisonous, while the others are more dangerous; it is less irritant and caustic than carbolic acid. All three dioxybenzols are excreted in the urine in combination with sulfuric and glycuronic acids. They are in part subjected to further oxidation, leading to coloration of the urine similar to that seen in carbolic acid poisoning.

Resorcin is applied in ointment (5 to 10 per cent) in skin diseases. The monoacetate of resorcinol **(euresol)** is milder and more prolonged in its action which is due to the gradual liberation of resorcin. It also does not discolor gray or blond hair. Like resorcin it is used as an adjuvant in the treatment of acne, seborrhea, rosacea and pityriasis steatoides.

PREPARATION

U. S. P., B. P.

RESORCINOL, resorcin, metadioxybenzol ($C_6H_4(OH)_2$), colorless, very soluble crystals with a faint aromatic odor. Dose, B. P., 0.06 to 0.3 gram.

5. Tar

Long before carbolic acid and its congeners were known, tars and other crude preparations enjoyed a reputation in the treatment of wounds, and some of these have been retained in medicine and are widely used. Among these the tar obtained by the dry distillation of different woods is included; its constituents vary with the source, but the creosols ($C_6H_3CH_3.OH.OCH_3$), guaiacols ($C_6H_4OH.OCH_3$), and other less poisonous aromatic compounds are present in larger quantity than the phenols and dioxybenzols, and wood-tar is therefore less poisonous than carbolic acid, and its simpler homologues. At the same time these higher combinations seem to have the same antiseptic powers as the simpler benzol derivatives, so that several of the crude preparations are used in surgery and medicine.

Therapeutic Uses.—Tar is used widely in a variety of skin diseases, in which it may be applied either alone or as an ointment. It is only

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slightly irritating to the skin, and some absorption occurs, as is often seen by the dark color of the urine. Internally it has been used occasionally as an "expectorant" in cough mixtures. Whether it has any effects on the lungs in these cases may be questioned. In combination with sulfur, tar is extensively employed in dermatological practice in the form of Wilkinson's salve.

PREPARATIONS

U. S. P.

PIX PINI, pine tar, a viscid blackish brown liquid obtained by the destructive distillation of *Pinus palustris* and other species of *Pinus*.

UNGUENTUM PICIS PINI, tar ointment containing 50 per cent pine tar.

OLEUM PICIS RECTIFICATUM, rectified oil of tar, a volatile oil from pine tar rectified by steam distillation.

SYRUPUS PICIS PINI, syrup of pine tar, a 0.1 per cent solution of rectified oil of tar in syrup.

B. P.

PIX LIQUIDA, tar. Dose, 0.12 to 0.6 gram.

6. Sulfur and Sulfur Containing Compounds

Sulfur is used largely in the treatment of parasitic infestations of the skin and in disorders of the sebaceous glands. Precipitated sulfur as a powder or incorporated in an ointment base is used for its keratoplastic, keratolytic and stimulative effects. An ointment containing 5 to 15 per cent sulfur is used in the treatment of scabies. Stronger applications are used in chronic eczema and other chronic disorders of the skin.

Ichthammol, a preparation of sulfoichthyolic acid was introduced as a substitute for ichthyol. It is obtained by distillation of bituminous schists, sulfonating the distillate, and neutralizing the product with ammonia. It is used in dermatologic conditions where a sulfur action is desired, as in rosacea.

Thigenol, a solution of sodium sulfo-oleate and naftalan, a distillate product of a crude naphtha from the Caucasus, are also used in dermatological practice.

Sulfoichthyolate preparations are salts of a mixture of sulfur containing acids derived from the tar of a bituminous shale. The ammonium compound of sulfoichthyolic acid was introduced as ichthyol (in allusion to the fact that the shale from which it is derived is the remains of fossil fishes). Applied to the skin, ichthyol causes slight irritation, which is apparently of benefit in some cutaneous diseases, and it has therefore been used extensively for this action. In more dilute form it possesses a demulcent or emollient effect. A certain amount of absorption occurs when it is rubbed into the skin, for the sulfur of the urine has been found to be augmented. Ichthyol has been strongly recommended in the treatment of a number of skin diseases. It is generally used as an ointment containing equal parts of ichthyol and petrolate, but may be used in 10 per cent or even weaker dilution.

PREPARATION

B. P.

ICHTHAMMOL, ammonium ichthosulphonate. Dose, 0.3 to 0.6 gram.

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7. Balsams

Another ancient treatment of wounds comprised the application of various balsams and some of these still maintain a position in therapeutics, though with increasing difficulty. Balsams are mixtures of resin, volatile oil, benzoic and cinnamic acids and their esters. The chief survivors are *Benzoin*, obtained from Styrax Benzoin and other species, *Styrax* from Liquidambar orientalis, *Balsamum Peruvianum* from Toluifera Pereiræ or Myroxylon Pereiræ and *Balsamum Tolutanum* from another species of the same genus.

Benzoin and Balsam of Peru are applied in parasitic skin diseases, notably in scabies. And the compound tincture of benzoin (containing benzoin, styrax, aloes, and balsam of Tolu) is still used in doses of 2 cc. (30 min.) as an ingredient of expectorant mixtures where the mucus is tenacious and coughed up with difficulty. It was formerly known as traumatic balsam and resembles in composition a number of old remedies which were known as Friar's balsam, Turlington's balsam, Jesuit's drops, etc. Syrup of Tolu is used merely as a flavoring agent.

Many other drugs applied to the skin may exercise some germicidal action along with their other properties, but are discussed elsewhere. (See Zinc, Lead, Sulfur Ointments.)

PREPARATIONS

U. S. P.

BALSAMUM PERUVIANUM, balsam of Peru, a dark brown viscid liquid with an agreeable odor.

BENZOINUM, benzoin, a resin obtained from various species of Styrax.

TINCTURA BENZOINI, a 20 per cent alcoholic solution of benzoin.

TINCTURA BENZOINI COMPOSITA, contains benzoin, aloe, storax and tolu balsam.

STYRAX, storax, a grayish brown sticky mass with a characteristic odor and taste.

BALSAMUM TOLUTANUM, balsam of Tolu, a brown or yellowish brown, plastic solid with a pleasant aromatic odor.

SYRUPUS BALSAMI TOLUTANI, a solution of tincture of Tolu balsam and magnesium carbonate in syrup.

TINCTURA BALSAMI TOLUTANI. Dose, 2 cc. (30 min.).

B. P.

BALSAMUM PERUVIANUM. Dose, 0.3 to 1 mil. (5 to 15 min.).

BALSAMUM TOLUTANUM. Dose, 0.3 to 1 gram.

SYRUPUS TOLUTANUS, syrup of Tolu. Dose, 2 to 8 mil. (30 to 120 min.).

TINCTURA TOLUTANA, tincture of Tolu. Dose, 2 to 4 mil. (30 to 60 min.).

BENZOINUM, benzoin. Dose, 0.6 to 2 grams.

TINCTURA BENZOINI COMPOSITA, compound tincture of benzoin or Friar's balsam. Dose, 2 to 4 mil. (30 to 50 min.).

STYRAX. Dose, 0.6 to 2 grams (10 to 30 gr.).

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III. GENITO-URINARY ANTISEPTICS

Prior to the introduction of the sulfonamides and antibiotics numerous compounds were used as genito-urinary antiseptics. Of these, the

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volatile oils (oils of copaiba, cubebs and sandalwood), hexylresorcinol, sodium salicylate, salol (phenyl salicylate), benzoic acid, ammonium benzoate, boric acid and borax are now only of historic interest.

It is very probable that with the availability of an antibiotic such as streptomycin which is effective against gram-negative bacteria, the use of such genito-urinary antiseptics as methenamine, mandelic acid and the dyes will also be relegated to oblivion. At present they are still used in infections not amenable to sulfonamide or penicillin therapy.

1. Hexamethylenetetramine, Methenamine, Hexamine

Hexamethylenetetramine ($(CH_2)_6N_4$), official as **methenamine** (U. S. P.) and **hexamine** (B. P.) has no important action itself, but is of interest from its liberating formaldehyde in the course of its excretion in the urine; formaldehyde is a powerful disinfectant, and the small quantities liberated from methenamine are sufficient to prevent putrefaction of the urine for many hours. Under certain conditions, microbes in the urine decrease in number or sometimes disappear altogether within a few hours of its administration. Formaldehyde is formed from methenamine only in the presence of acid and the only fluids in the body which are acid enough to liberate it are the gastric juice and the urine. A certain amount of the drug swallowed is decomposed in passing through the stomach, but enough is absorbed unchanged to act in the urine if it is acid; when it is alkaline, methenamine has no disinfectant action in the urinary passages; when, however, in those cases the reaction of the urine is rendered acid by the administration of acid phosphates or ammonium chloride or nitrate, formaldehyde is formed from methenamine and satisfactory results follow. It follows therefore that in order that the treatment with methenamine be successful the pH of the urine shall be controlled and should in general be kept below 5.6. No symptoms arise from ordinary doses of methenamine, but large quantities have occasionally given rise to gastric discomfort and to pain and discomfort in the bladder, and more rarely to hematuria; the irritant here is not the unchanged drug but the formaldehyde liberated by it.

Therapeutic Uses.—Methenamine is used in cystitis and urethritis where the infecting organism is not responsive to the available sulfonamide or antibiotic preparations (p. 725). In order to ensure that the urine shall be acid, methenamine is often given along with acid sodium phosphate (1 gram), ammonium nitrate or ammonium chloride.

Preparations

U. S. P.

Methenamina, methenamine, a white crystalline powder. Dose, 0.5 gram.
Tabellæ Methenaminæ. Dose, 0.5 gram.

B. P.

Hexamina, hexamine, methenamine. Dose, 0.6 to 2 grams.
Tabellæ Hexaminæ, tablets of hexamine, methenamine tablets. Dose, 0.6 to 2 grams.

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2. Mandelic Acid

Since acid urines are less favorable for the growth of bacteria, attempts were made to utilize a high fat, low carbohydrate diet to produce a state of ketosis in order to control urinary infections. The results were so successful that the simpler method of inducing the same condition by the use of a low caloric or starvation diet was employed to avoid the difficulties associated with the ketogenic diet first used. It was soon pointed out by Rosenheim that while the results thus obtained by these diets were due to the beta-hydroxybutyric acid, the method of attaining this end was unnecessarily complicated and could be reached by the more direct means of administering an acid at once. It was not feasible to administer the hydroxybutyric acid itself by mouth because when given in this manner it is largely oxidized to carbon dioxide and water before reaching the kidney. From the various organic acids which were studied, mandelic acid was selected as being most suitable for the purpose, inasmuch as it is relatively non-toxic and is excreted unchanged by the kidneys.

Mandelic acid (alpha-hydroxy-alpha-toluic acid) is a white crystalline powder relatively soluble in water (16 per cent at 20°) and is usually given dissolved in water in doses of 3 grams four times daily. The sodium salt has been used, but the ammonium salt has largely replaced it.

In order to insure its greatest degree of effectiveness several precautions are necessary. The fluid taken by the patient should be restricted to 1,200 cc. per day and the pH of the urine must be observed daily and kept below 5.6. If the desired degree of acidification is not attained it may be necessary to give some drug such as ammonium chloride. If these conditions are obtained the urine usually becomes bactericidal in two or three days and free from infection in six or seven. It is seldom necessary to continue this therapy longer than ten or twelve days and indeed it is inadvisable to do so because of the possibility of renal irritation. In some patients a return of the infection has been seen after the drug has been stopped and in such cases it may be necessary to repeat the treatment after allowing a rest interval of a week or two.

The administration of the drug produces at times nausea but rarely does it cause diarrhea. It also may cause renal irritation with the presence of hyaline casts. Small numbers of red blood cells are found in the urine at times and more rarely gross hematuria. The drug is contraindicated in cases of renal insufficiency as it might act as an additional source of irritation to the kidney and in addition it might not be excreted in sufficient amounts to make the urine bactericidal.

The use of mandelic acid is reserved for cases in which the infecting organism is resistant to the sulfonamide and antibiotic drugs. Culture of the urine is necessary before one can conclude as to the best agent to be employed in a given case.

Preparation

U. S. P., B. P.

Acidum Mandelicum, mandelic acid, a white crystalline powder. Dose, U. S. P., 3 grams; B. P., 2 to 4 grams.

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IV. DISINFECTANTS FOR ROOMS, FURNITURE, ETC.

1. Formaldehyde

Formaldehyde (HCHO), the aldehyde derived by oxidation from methyl alcohol, is a very powerful germicide, while it is not very dangerous to the higher animals. The aldehyde is a colorless gas and has been used either in solution in water (*formalin*) or as a vapor. As a germicide it is estimated to be as efficient as corrosive sublimate, and its volatility enables it to penetrate much more rapidly so that it may be used for purposes for which the latter is unsuitable.

Action.—The vapor is very irritant when inhaled, causing stinging and prickling in the nose and throat, salivation and tears, and bronchial irritation and catarrh. In the few cases of poisoning in man recorded, the symptoms were those of gastric irritation and consequent collapse. When swallowed by animals the watery solution produces nausea and vomiting, which are followed by narcosis, coma, and in the rabbit by convulsions and opisthotonos. The respiration in the dog is very greatly accelerated some time before death, while in the rabbit this is not as marked or is entirely absent. The blood-pressure is increased at first, and the heart is slow from direct action on the cardiac muscle. Formaldehyde is rapidly absorbed from the alimentary tract and also by the lungs but quickly disappears from the blood owing to its oxidation and excretion; some formic acid is said to be formed from it, and formaldehyde has been detected in the urine, the gastro-intestinal secretions, and the expired air.

The powerful action of formaldehyde on microbes and on mucous membranes is believed by Loew to be due to its combining with the amino groups in the proteins, and as a matter of fact, a number of changes have been described in the reaction of proteins exposed to this gas. For example, egg albumen and serum to which formaldehyde solution has been added are not precipitated by heat and are less easily digested by ferments, while casein is not coagulated by the rennet ferment. Some of the ferments (pepsin and diastase) are not affected by small amounts of formaldehyde, while trypsin and papain lose their activity wholly or in part.

Uses.—Formaldehyde is too irritant to admit of its use as an antiseptic in medicine and surgery, but it has been largely employed to disinfect instruments, furniture, clothes and rooms, which cannot be sterilized by heat. Diluted liquor (4 per cent) may be used for some of these purposes, or the vapor may be disengaged by distillation from the liquor or by heating paraform. Large rooms filled with formaldehyde

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vapor and left for some hours are found to be almost completely sterilized, so that cultures of the pathogenic microbes exposed in them cease to grow even when removed from the atmosphere. The odor of formaldehyde may be removed by sprinkling ammonia solution with which it forms hexamethylenamine. The disinfectant action of formaldehyde is increased by moderate warmth, and a longer time must be allowed for it to act if the temperature of the room is below 50° F. Formaldehyde not only destroys the microbes, but also alters the toxins formed by them so that they are no longer poisonous, even in very large quantities.

Preparation

Liquor Formaldehydi (U. S. P., B. P.), formalin, a solution of formaldehyde in water containing not less than 37 per cent of the gas, which may be obtained from it by distillation.

2. Sulfur Dioxide

Sulfurous acid is a powerful reducing agent, as it becomes oxidized to sulfuric acid, and this renders it poisonous to protoplasm in general, quite apart from its acidity. Sulfurous acid anhydride has accordingly been used occasionally to disinfect rooms and furniture after infectious diseases; for this purpose sulfur is burned in the room, which ought to be rendered as air-tight as possible, and the fumes are allowed to act for several hours before the room is ventilated. The value of this method of disinfection has been called in question, and though sulfurous acid gas is fairly germicidal when it is applied along with moisture, it may be doubted whether it has ever been used efficiently in practice; unless efficient, the procedure is open to the objection that it may lend a sense of security which is quite unwarranted, and may lead to the neglect of other measures. Sulfur dioxide bleaches and rots most materials, and the fumes are fatal to the higher animals, even when much less concentrated than are necessary to destroy bacteria. In order to be of service, at least 1 volume of SO_2 ought to be present in each 100 volumes of air, and even this concentration is insufficient to destroy the spores of bacteria.

The chief symptoms of **poisoning** with sulfurous acid solution are those of irritation of the mucous membranes, and if the solution is swallowed these may not differ from those of other irritants.

In poisoning from the inhalation of the anhydride, the symptoms arise chiefly from the respiratory tract. Even in a dilution of 1:2,000 it acts as an irritant, causing sneezing, coughing and lacrimation, and in somewhat greater concentration it becomes entirely irrespirable; smaller quantities in the air cause bronchial irritation and catarrh, when inhaled for some time. Sulfurous acid is neutralized and oxidized for the most part to sulfates in the tissues, or probably partly in the course of absorption.

Sodium sulfite (Na_2SO_3) and thiosulfate or hyposulfite ($Na_2S_2O_3$) are rapidly changed to the sulfate when given by the mouth; the liberation of SO_2 in the stomach may cause some gastro-intestinal irritation in man, and in animals

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vomiting has occurred from it. Injected subcutaneously in the frog they cause muscular weakness and finally central nervous paralysis; in the cat and dog a preliminary stage of vomiting, dyspnea and restlessness is seen, apparently from direct action on the center in the medulla and on the heart and vessels. When applied in this way the sulfite is excreted in the urine as sulfate, while the thiosulfate is changed more slowly and from a third to a half may escape by the kidneys unchanged.

3. Chlorine and Bromine

Chlorine and bromine resemble each other closely in the effects which they induce in all forms of living matter. These may be explained in part by their replacing hydrogen in its combinations in the proteins and forming hydrochloric or hydrobromic acid with the hydrogen set free, in part by their combining with the hydrogen of water and thus liberating oxygen, which then acts on the tissues. These processes are believed to account for the fact that chlorine is a much more powerful disinfectant in moist air than in dry. In the higher organisms all of these reactions probably occur together.

Action.—Chlorine and bromine are general protoplasm poisons; thus 3 parts of chlorine in 1,000 parts of moist air are sufficient to destroy the spores of most bacteria in the course of three hours, and the infusoria and the higher plants have been shown to be equally susceptible to the influence of the gas. Even smaller quantities of bromine are disinfectant.

In the higher animals and in man chlorine and bromine act as irritants, causing irritation and redness and even blistering of the skin when applied to it in solution, and eliciting when swallowed intense inflammation and corrosion of the mouth, throat, and stomach, with collapse and all the ordinary effects of gastric irritation. Air containing 1 part of chlorine in 100,000 irritates the eyes, nose, larynx and the deeper respiratory passages; bronchitis, pulmonary congestion and hemorrhages, coughing and pain in the thorax are induced by somewhat higher concentrations, and exposure to about 1 part in 3,000 for fifteen minutes causes acute edema of the lungs, which may prove fatal immediately. More dilute vapor may be equally dangerous if the exposure is longer. Chlorine and bromine as such are not used in therapeutics, but have given rise to poisoning in their industrial use, and the former has more recently acquired notoriety from its being used in warfare.

These symptoms of chlorine and bromine poisoning are caused by their local action only; they are changed to hydrochloric and hydrobromic acids, and these again to chlorides and bromides in the course of absorption. Attention has been drawn to a number of cases in which symptoms arose in workmen in chemical factories where chlorine is liberated by electrolysis, or more rarely in others where hydrochloric acid is formed in large quantities. The most marked symptom is an affection of the sebaceous glands, from which the condition receives its name of chlorine acne, but this often induces headache, sleeplessness, loss of appetite, and anemia. No satisfactory explanation of the symptoms has been given, nor is it known whether the chlorine or some unknown body is the cause (Lehmann, Jacquet).

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The **Hypochlorites** disengage chlorine more slowly than solutions of chlorine and are correspondingly less toxic to microbes and the higher forms of life. (See p. 799.)

The chlorine preparations are chiefly used to disinfect feces, urinals and to a less extent rooms and houses; for this purpose chlorinated lime is the most suitable, especially when acid is added to it in excess. The room ought to be hermetically sealed, and the fumes are of no value as disinfectants unless they are present in such quantity as to render the air quite irrespirable. They have the disadvantage that they bleach most of the colors used in dyeing, and fail to penetrate in sufficient quantity into the clothing, which they also corrode to some extent. Chlorinated lime exposed in the sick-room serves merely as a deodorant, and has no disinfectant value, but has the disadvantage of giving a false feeling of security like other similar measures. Chlorine seems inferior to sulfurous acid anhydride, and still more so to formaldehyde as a disinfectant, not from its being weaker in action, but because it is more difficult to apply in sufficient quantity. Chlorinated lime can, however, be applied in urinals and closets, where both these disinfectants are unavailable. Here again it acts as a deodorant, while its disinfectant value is smaller. Chlorine gas is used principally in the purification of drinking water and swimming pools.

Chlorine in the form of hypochlorite has proved effective in destroying the germs in drinking water; it should be added in such amount as to leave about 1 part of free chlorine in 1,000,000 of water. Several compounds have been introduced for this purpose. **Halazone** (para-sulphone dichloramido-benzoic acid) ($Cl_2N.O_2SC_6H_4COOH$) is efficacious in about 4 parts per 1,000,000 and is more stable and more easily transported in small quantities than the hypochlorites. In the presence of alkaline carbonates, borates, and phosphates it will sterilize in thirty minutes water contaminated with typhoid and other bacilli when used in the strength of 4 to 8 mg. per liter. Tablets containing halazone and the necessary carbonate are available commercially.

Succinchlorimide, the chlorinated imide of succinic acid ($C_4H_4O_2HCl$) is available for the same purpose. The addition of 11.6 mg. of this drug is said to disinfect a liter of water within twenty minutes.

4. Other Disinfectants

Many other substances may be employed as disinfectants of urinals, latrines, feces, etc., the chief determining consideration being the cost of the material in most cases. Thus tar, or crude carbolic acid may be used to disinfect fecal matter, and unslaked lime is applied to bodies in epidemics in the hope of preventing the liberation of infectious organisms. The most certain disinfectant, where it is available, is moist heat which is generally used to disinfect clothes and bedding which have been in contact with infected persons.

For the disinfection of the air, various aerosols containing glycol vapors and ultraviolet light have also been used.

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5. The Insecticides

Although these agents are not usually classified as antiseptics or disinfectants, they nevertheless may be considered here for like the former, these substances eliminate the agents causing disease by destroying the carriers of these pathogens. Insecticides have assumed an important rôle in the eradication of disease and by their use many insect-borne epidemics may be prevented. The introduction and use of these compounds during the Second World War was probably of much greater importance in practical medicine than the innovations in the use of the local antiseptic and disinfectant agents.

DDT (Dichlorodiphenyltrichloroethane) although synthesized over seventy years ago was only discovered to have potent insecticidal power in agriculture in 1939. Its efficiency in destroying flies, mosquitoes, lice and other carriers of human disease was later noted and its use during the second World War to destroy the body louse undoubtedly averted serious typhus epidemics.

DDT is characterized by its prolonged action compared to other insecticides, being effective for many weeks after its application. It kills insects on contact by poisoning their nervous system. When impregnated into clothing its effects last for as long as a month in spite of repeated washes. Its use in this way averted a threatening typhus epidemic in the winter of 1943–44 at Naples. More than a million people were dusted with the insecticide in this area to avert the threatened epidemic. Thus, the ravages of typhus which, during and following the first World War caused more deaths than any other single cause including battle casualties, were largely eliminated during the more recent holocaust.

DDT should not be used indiscriminately since it is more toxic than was originally suspected. Its toxic effects in man and other mammals is still a subject of study.

Pyrethrum, the widely used insecticide derived from pyrethrum flowers (*Chrysanthemum cinerariæfolium*) is used in medicine in the form of an ointment in the treatment of scabies. This penetrates the burrows and kills both the mites and eggs. Only rarely is dermatitis with exfoliation or allergic sensitivity to the drug observed.

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PART VI

Vaccines, Sera and Miscellaneous Biologicals

THE prophylactic and therapeutic use of vaccines, toxins, and antitoxins has assumed an important place in modern therapeutics for their use makes possible the prevention of otherwise serious disorders, the attenuation of others and the detection of the presence or susceptibility to certain diseases. These complex biologicals have become of increasing importance in the diagnosis, prevention and treatment of disease. Although primarily a subject for consideration in bacteriology and immunology, a very brief account of these agents may be given here since they now find a place in our Pharmacopeias.

Because of their potentially dangerous character and the need of their control as regards potency and efficacy, the sale of viruses, serums, toxins and analogous products is under stricter governmental control than is the case with other medicinals. No product of this category may be exported or sold in interstate commerce except by license of the United States Public Health Service. Each package of these biologicals must bear an expiration date in order to avoid the use of deteriorated materials. They must undergo official potency tests and be preserved against bacterial contamination by the addition of cresol (0.4 per cent), phenol (0.5 per cent), glycerin, organic mercurials or other antiseptic.

1. VACCINES, TOXINS AND TOXOIDS

It has long been known that spontaneous recovery can occur in man and in the lower animals from diseases now proved to be due to infection by pathogenic organisms. It was also early recognized that one attack of such disease might confer a partial or complete insusceptibility to subsequent infection. Thus a person who had suffered from an attack of smallpox was very unlikely to have a second attack, however much he might be exposed to infection. There would be no gain, however, in artificially subjecting a person to such a disease, merely to prevent a second attack, as obviously he would run all the usual risks and would be compelled to undergo a disease which in the normal course of events he might have escaped. It was a great and fruitful advance when Jenner showed that a person who had suffered from cowpox—a disease closely allied to, but much less severe than, actual smallpox—was less susceptible to smallpox itself. In other words, cowpox infection conferred an immunity against smallpox, as shown by the fact that a person who had had cowpox was less likely to acquire smallpox, or, if he did acquire the latter disease, suffered from it in a milder form. Advantage is taken of this fact in "**vaccination**" against smallpox. This is done by means of vaccine lymph, which is obtained from the vesicles produced

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by inoculation of vaccine virus on the skin of healthy animals. One minim of the lymph is applied by scarification to the skin, *e. g.*, of the arm or leg. This produces the local and constitutional reactions typical of cowpox and confers a high degree of immunity, lasting with diminishing intensity for many years, against smallpox infection.

In vaccination against smallpox, the virus of a related disease only mildly pathogenic to the human is used to induce immunity to the more serious human ailment. Active immunization may also be induced by injecting (1) attenuated living viruses or killed viruses, (2) bacterial toxins, (3) modified bacterial toxins and (4) bacterial vaccines.

Rabies vaccine is an example of the use of an attenuated or killed virus in the prevention of dreaded hydrophobia. Pasteur discovered that the virus of the disease is present in the central nervous system of animals which have suffered from it, and that a suspension of such tissue, suitably prepared, can be used as a vaccine for prophylaxis of the disease. In practice the vaccine is used chiefly to confer an active immunity against rabies in cases of known or suspected infection, and this is possible owing to the relatively long incubation period. The attempt is made to render the bitten person sufficiently immune during this period to confer protection against the disease before the virus has had time to affect the nerve conters.

Scarlet fever streptococcus toxin is an example of a bacterial toxin used to induce immunity. The pathological disturbances of structure and function resulting from infection by pathogenic organisms are as a rule due not so much to mechanical or other effects of the bacteria themselves as to the action of toxins which they form. These toxins may act locally and generally. Escaping into the blood they may produce effects on organs remote from the actual seat of infection. The process of recovery of an animal from a bacterial disease is accompanied by the appearance in the blood and tissues of "**antibodies,**" which in various ways inactivate the bacteria or neutralize their toxins. Antibody formation is not a reaction peculiar to bacteria or toxins but occurs when any foreign protein is injected. It is a reaction which occurs to all proteins and proteoses and to these only. It does not occur readily if at all when they are given by mouth, because the proteins are broken down by digestive processes in the alimentary canal into amino-acids which do not provoke this reaction. Antibody formation is one of the most important natural mechanisms for resisting invasions of bacteria or for neutralizing the protein-like toxins which they produce. It is perhaps the most general method by which a bacterial disease is overcome and "**immunity**" to it acquired. When an animal acquires immunity to bacteria or their toxins by being exposed naturally or artificially to their actions, the immunity so acquired is called "active immunity" because the animal manufactures its own antibodies, and the immunity so acquired may be lasting, depending upon the duration of antibodies in the tissues and other factors.

Active immunity against toxins may also be induced by injection of attenuated or modified **toxins.** Various methods are in use for reducing the virulence of a toxin without destroying its power of provoking

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immunity. This can in some cases be successfully achieved by the addition to the toxin of the specific antitoxin. This procedure is adopted in the case of **diphtheria toxin-antitoxin** mixture. The addition of formaldehyde or other chemical agents may also modify a toxin in such a way as to render it non-toxic without interfering with its capacity to induce immunity reactions. Diphtheria **toxoid**, alum precipitated diphtheria toxoid, staphylococcus toxoid and tetanus toxoid are examples of such preparations. Diphtheria and tetanus toxoid may be combined and injected together for routine administration to infants as a prophylactic against these formerly common and dangerous diseases.

The use of bacterial **vaccines** depends upon the fact that injected bacteria, even when they are killed, can still provoke immunity. Immunization with dead bacteria can often be induced with relatively little risk or even inconvenience, because the organisms cannot multiply in the body and a safe but effective immunizing "dose" can be found by experience. Such a vaccination is used as a prophylactic against typhoid fever. There are at least three bacilli, *viz.*, *B. typhosus*, *B. paratyphosus A*, and *B. paratyphosus B*, which are responsible for different kinds of typhoid fever. Though these bacilli are closely allied, an attack due to infection by one of them will not confer immunity against the others. By the use of a vaccine containing all three a person can be simultaneously immunized against them all. This is now the usual practice. Typhoid-paratyphoid vaccine is a standardized sterile suspension of these three bacilli which have been killed by heat. Three doses are usually given by subcutaneous injection, one of 0.5 cc. and the second and third of 1 cc. at weekly intervals thereafter. Such vaccination has been practiced on a large scale in many countries and has done much to lessen the incidence and gravity of typhoid fevers. Its routine use in armies has, with improved sanitation, practically wiped out what was formerly a scourge of all wars.

Other bacterial vaccines have been prepared from the acne bacillus, from Brucella organism, from the cholera vibrio, the plague bacillus and from staphylococci.

The discovery that many viruses multiply when implanted on the allantoic membrane of the incubating egg has led to the use of this procedure for the preparation of vaccines for use against virus diseases. Vaccines have been prepared from such cultures for epidemic typhus, influenza, measles and other viral diseases but their efficacy as prophylactics is still not firmly established.

Preparations

U. S. P.

Vaccinum Rabies, rabies vaccine. Average dose: the contents of one container, to be repeated at proper intervals.

Vaccinum Typhosum, bacterial vaccine made from the typhoid bacillus. Average dose, by hypodermic injection, 0.5 cc. and 1 cc., the latter dose to be repeated once.

Vaccinum Typho-paratyphosum, bacterial vaccine made from the typhoid bacillus and the paratyphoid "A" and "B" bacilli. Average dose as for Vaccinum Typhosum.

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VACCINUM VARIOLÆ, smallpox vaccine.

TOXINUM DIPHTHERICUM DETOXICATUM, diphtheria toxoid. Average dose by hypodermic injection, prophylactic, 1 cc.

TOXINUM SCARLATINÆ STREPTOCOCCICUM, scarlet fever streptococcus toxin. Prophylactic injection, for active immunization, graded hypodermic doses at proper intervals until a negative Dick test is obtained.

TOXOIDUM DIPHTHERICUM, diphtheria toxoid. Also in the form of: diphtheria toxoid, alum precipitated. Average dose, for active immunization, 1 cc. repeated at proper intervals until a negative Schick test is obtained.

TOXOIDUM TETANICUM, tetanus toxoid. Also in the form of: tetanus toxoid, alum precipitated. Average dose, for active immunization, 1 cc. hypodermically to be repeated at proper intervals.

B. P.

VACCINUM VACINNIÆ, vaccine lymph. Dose, 0.06 mil.; 1 min., by scarification.

VACCINUM TYPHO-PARATYPHOSUM, antityphoid-paratyphoid vaccine; by subcutaneous injection, 0.5 mil. (first dose), 1 mil. (second dose after seven to ten days interval).

TOXINUM DIPHTHERICUM DETOXICATUM, diphtheria prophylactic. The requisite dose is indicated on the label and is given by subcutaneous injection on two or three occasions at intervals of two to four weeks.

TOXINUM TETANICUM DETOXICATUM, tetanus toxoid. Dose, subcutaneously or intramuscularly, 0.5 to 1 mil.

2. ANTITOXIC SERA, IMMUNE SERA AND ANTITOXINS

As has already been explained, natural cure of many bacterial diseases results largely from the formation in the tissues of **antibodies** which inhibit the multiplication of bacteria or neutralize their toxins; and especially for prophylaxis, artificial immunity can be actively induced by suitable injections of attenuated bacteria or toxins. When a bacterial infection is severe or if the patient has a low resistance to it, antibody formation may not take place sufficiently rapidly or adequately to save the patient from the effects of the toxins. Once the toxin has combined with the tissues, antitoxin is incapable of dislodging it. It would be clearly of advantage, therefore, if the patient could be quickly supplied with the necessary antitoxin from extraneous sources. This can be done by injecting antitoxin obtained from a horse or other suitable animal which has been immunized against the toxin. The details of procedure for obtaining antitoxin varies in the case of different toxins. Generally, however, a horse is immunized by repeated injections of the toxin at intervals of a few days for a period of several months until the blood acquires a sufficiently high antitoxin content. The animal is then bled and separated serum collected and standardized according to its power of neutralizing toxin. This power is expressed in "units" compared with a standard antitoxic serum. The serum may be used as such or as the separated globulins, which contain practically all the antitoxins. A person can be immunized against a toxin by an injection of such an antitoxic serum. Immunity conferred in this way is called "passive immunity" because the person does not manufacture his own antitoxins as a personal reaction to the toxin but receives the antitoxin ready made. Immunity passively produced in this way is more transient and usually less complete than active immunity, but has the advantages of speed and safety of induction. Antitoxins are used both as prophy-

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lactic and curative agents. In the latter case their value depends largely upon their being given sufficiently early and in sufficient doses, so that the toxin can be neutralized before it combines with the tissues and before it produces its toxic effects.

Serums can also be obtained to combat bacteria themselves, in which case the serum is obtained by immunizing a horse or rabbit against the particular bacterium and is used in much the same way as an antitoxic serum. Of such serums those which have proved most successful in treatment are **antimeningococcus serum** and **antipneumococcus serum**, both of which were widely used until the advent of the sulfonamide and antibiotic drugs. At present they are little used except in the most severe cases or in patients who fail to react to the chemotherapeutic measures.

The available antitoxins and antitoxic serums include:

Crotalus (antivenin) antitoxin or North American anti-snake bite serum
Botulism antitoxin
Diphtheria antitoxin
Erysipelas streptococcus antitoxin
Gas gangrene antitoxin
Tetanus antitoxin
Tetanus-gas gangrene antitoxin
Scarlet fever antitoxin
Staphylococcus antitoxin
Antianthrax serum
Antidysenteric serum
Antierysipelas serum
Antierysipeloid serum
Antimeningococcic serum
Antipneumococcic serum, type specific

Immune serums may in certain cases also be obtained from human beings convalescing from the specific infectious disease. The most important of these is human measles and scarlet fever immune serum. The antibodies effective against measles are also present in the human placenta and may be obtained from this source. Human immune globulin is also useful in the prevention and modification of measles, being equivalent in usefulness to convalescent serum.

Preparations

U. S. P.

Antitoxinum Diphthericum, diphtheria antitoxin. Average dose by parenteral injection: therapeutic, 20,000 units; prophylactic, 1,000 units.

Antitoxinum Scarlatinæ Streptococcicum, scarlet fever antitoxin. Average dose, by parenteral injection: therapeutic, 6,000 units; prophylactic, 2,000 units.

Antitoxinum Tetanicum, tetanus antitoxin. Average dose by parenteral injection: therapeutic, 20,000 units; prophylactic, 1,500 units.

Serum Antimeningococcicum, antimeningococcic serum. Average dose by parenteral injection, therapeutic, 20 cc.

Serum Antipneumococcicum, antipneumococcic serum, Type Specific. Average dose, by parenteral injection, therapeutic from 20,000 to 100,000 units.

Serum Immune Morbillosi Humanum, human measles immune serum. Average dose, therapeutic, 20 cc.; prophylactic, 10 cc.

Serum Immune Scarlatinæ Humanum, human scarlet fever immune serum. Average dose, therapeutic, 20 cc.; prophylactic, 10 cc.

B. P.

Antitoxinum Diphthericum, diphtheria antitoxin. Doses by injection: prophylactic, 500 to 1,000 units; therapeutic, 10,000 to 20,000 units.

Antitoxinum Œdematiens, gas-gangrene antitoxin (œdematiens). Doses by injection: prophylactic, 20,000 units; therapeutic, 50,000 to 100,000 units.

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ANTITOXINUM STAPHYLOCOCCICUM, staphylococcus antitoxin. Doses by injection, 5,000 to 20,000 units.

ANTITOXINUM TETANICUM, tetanus antitoxin. Doses, by injection: prophylactic, 1,000 to 2,000 units; therapeutic, 20,000 to 40,000 units.

ANTITOXINUM VIBRIO SEPTICUM, gas-gangrene antitoxin (vibrion septique). Doses by injection: prophylactic, 5,000 units; therapeutic, 10,000 to 20,000 units.

ANTITOXINUM WELCHICUM, gas-gangrene antitoxin. Doses, prophylactic, 4,000 units by injection; therapeutic, 10,000 to 20,000 units by intravenous injection.

SERUM ANTIDYSENTERICUM (SHIGA), antidysentery serum. Doses by injection, 4,000 to 10,000 units.

SERUM ANTIPNEUMOCOCCICUM I, antipneumococcus serum (Type I). Doses by intravenous injection, 50,000 to 150,000 units.

SERUM ANTIPNEUMOCOCCICUM II. Doses similar to those for Type I.

3. NORMAL HUMAN BLOOD DERIVATIVES

The recognition of the importance of adequate blood volume has prompted the use of normal human serum in the treatment of shock and other conditions where there is a deficiency of the blood volume or blood proteins. In surgical and traumatic shock the loss of blood volume and hemoconcentration, with its attendant decrease in cardiac output leads to anoxia of the tissues and an irreversible state of shock which may be prevented by the administration of human plasma. This has the advantage over whole blood transfusion in that it requires no typing and can be maintained in a readily available form for immediate use when necessary.

Normal human plasma is available in the form of citrated plasma or serum. It may be dehydrated by rapid freezing and removal of its water content under high vacuum, the plasma being restored in its original concentration or as a hypertonic solution, if desired, by adding the requisite amount of water prior to use.

In addition to its use in surgical and traumatic shock, normal human plasma or serum are used in the treatment of burns, to combat hypoproteinemia and as a temporary substitute for whole blood where this is not available. By the fractionation of human blood it is possible to obtain a number of products which have therapeutic value. The albumin fraction may be separated thus giving a solution osmotically more active than plasma. The globulins may be used for their antibody content to induce immunity. The fibrin may be separated for use as an hemostatic agent or to form fibrinogen plastics which are tolerated by the tissues and may be used for the repair of dural or other defects.

Various colloidal solutions have been suggested as substitutes for human plasma but have not proved satisfactory partly because of their inadequacy for maintaining the blood volume but chiefly because of their toxicity. Among these blood substitutes may be mentioned gum acacia, purified albumin from beef blood, gelatin, pectin, periston, etc.

PREPARATION

U. S. P.

SERUM HUMANUM NORMALE, normal human serum. Average dose, 500 cc. intravenously.

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4. PROTEIN HYDROLYSATES

Proteins are the basic constituents of protoplasm and constitute one of the essential foodstuffs. In malnutrition, diseases of the liver, nephrosis and other conditions in which the synthesis of protein is deficient or excessive amounts are lost from the body, hypoproteinemia results. In this condition as well as in individuals in whom a readily available source of protein is desired, the use of protein hydrolysates is recommended. These may be administered either orally or parenterally and consist chiefly of amino acids, and low molecular polypeptid hydrolytic degradation products prepared by hydrolysis of mixtures of milk, beef, wheat and bean proteins. They furnish all of the essential amino-acids for the synthesis of tissue and blood protein in a readily assimilable form.

Protein hydrolysates or amino-acid preparations are available in powder form or as solutions for parenteral administration.

Among the specific amino-acids which constitute the protein molecule, methionine is of therapeutic interest because of its lipotropic action which has led to its use in cirrhosis of the liver and hepatitis. Its exact status in the therapy of these conditions is, however, still uncertain.

Reactions may be observed following the administration of protein hydrolysates intravenously although these are less apt to occur with some of the improved purified forms now available. It is possible by their use to maintain satisfactory nitrogen balance in patients who are able to take little or no protein by mouth or those who lose excessive amounts of nitrogen.

5. DIAGNOSTIC AGENTS

Several toxins, antitoxins, viruses and other protein derivatives of pathogenic organisms have been prepared for use as diagnostic agents. These depend for their action on the fact that the reaction to their intradermal injection is dependent on the state of immunity of the organism. Thus in the Schick test a specially prepared diphtheria toxin is injected intradermally. An area of redness at the site of injection will develop in individuals who are not immune to diphtheria. The use of scarlet fever streptococcic toxin is used in a similar way for the Dick test. The scarlet fever streptococcus antitoxic serum which is used to produce passive immunity in this disease is also used in the Schultz-Charlton skin test to differentiate the rash of scarlet fever from other eruptions. A disappearance of the rash at the site of injection is pathognomonic of scarlet fever.

Tuberculin, which is prepared in a variety of forms, is used as a diagnostic agent in persons suspected of having this disease. The mere existence of a positive reaction does not indicate that the subject has the disease in an active form. Patients with far advanced or rapidly progressive tuberculosis may, on the other hand, give a negative reaction. Tuberculin is used chiefly in large scale screen testing, a negative reaction indicating the absence of clinical tuberculosis, only those showing a positive reaction being subjected to roentgenological examination. Also in cases of suspected tuberculosis, the failure to give a positive reaction helps to exclude tuberculosis in the differential diagnosis.

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Other useful antigens used as diagnostic agents are the virus of lymphogranuloma inguinale (Frei test), and bacterial proteins derived from Trichinella and Coccidiomycosis used for detecting present or past infection with these organisms. In this connection mention may also be made of a variety of chemical agents which are used for determining the functional state of different organs. Thus the rate at which phenolsulfonphthalein is excreted following its injection is used as a kidney function test. The rate at which sodium sulfobromophthalein disappears from the blood is used as a test for liver function. Various compounds may be used for other clinical tests, but for the details of these the reader is referred to texts on laboratory procedures.

PREPARATIONS

U. S. P.

TOXINUM DIPHTHERICUM DIAGNOSTICUM, diphtheria toxin for the Schick test. Average dose, 0.1 cc. intracutaneously.

TOXINUM SCARLATINÆ STREPTOCOCCICUM, scarlet fever streptococcus toxin for the Dick test. Average dose, 0.1 cc. intracutaneously.

TUBERCULINUM PRISTINUM, old tuberculin. Average dose, diagnostic, 0.000,01 to 0.001 cc. intracutaneously; therapeutic, 0.000,000,01 to 0.000,001 cc. subcutaneously.

PHENOLSULFONPHTHALEINUM, phenolsulfonphthalein. Also available as Injectio Phenolsulfonphthaleini. Average dose, 6 mg., intramuscularly or intravenously.

SULFOBROMOPHTHALEINUM SODICUM, sulfobromophthalein sodium. Also available as Injectio Sulfobromophthaleini Sodici. Average dose, 2 mg. per kilogram of body weight, intravenously.

B. P.

TOXINUM DIPHTHERICUM DIAGNOSTICUM, Schick test toxin, and TOXINUM DIPHTHERICUM CALIFACTUM, both by intradermal injection. 0.2 mil. (3 min.).

6. VEGETABLE TOXALBUMINS: RICIN

Some albumins found in plants and of a highly poisonous nature resemble the toxins produced by bacteria both in their physiological actions and in their immunity reactions. Indeed, the investigation of their effects has played an important part in the advancement of knowledge of the corresponding effects of bacterial toxins. The most important of these vegetable toxins are Ricin, Abrine and Crotin, and they can be conveniently considered in juxtaposition to the bacterial toxins.

Ricin is an intensely poisonous albumin found in the seeds of Ricinus communis along with castor oil, which does not itself contain this principle, however. Ricin is poisonous in doses of about $\frac{1}{1000}$ mg. per kilogram body weight injected subcutaneously, but seldom causes any symptoms when swallowed, as it is apparently destroyed for the most part by the digestive ferments. It is thus among the most powerful of the vegetable poisons when it is injected subcutaneously. Death often occurs only several days after the injection in animals, and in the interval no symptoms make their appearance except some loss of appetite, and toward the end, diarrhea and vomiting. Postmortem, the bowel is found inflamed and congested and contains ecchymoses; blood is found in the serous cavities, and extravasations may occur in various other organs, although not so uniformly as in the bowel. Among the most obvious lesions are the innumerable ecchymoses in the great omentum and the swelling of the abdominal lymph glands, which generally contain numerous small hemorrhages.

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Microscopic examination reveals small foci of necrosed tissue in the liver, spleen, intestine, stomach, and other organs. Ricin seems to be excreted by the intestinal epithelium, which may explain the violence of its action here, although it acts as a poison in many other tissues. It is a powerful irritant, inducing inflammation and suppuration when it is injected subcutaneously, or is applied to the conjunctiva. On the other hand it has little or no irritant action on the mouth and throat, and is usually digested and rendered harmless in the stomach. The mucous membrane of the nose is irritated by the inhalation of the powder in many persons. This toxalbumin has a very characteristic action on the blood. When a drop of a dilute solution is added to a test-tube of defibrinated blood, the corpuscles soon fall to the bottom, leaving the clear serum above, and the blood does not filter through paper any longer, the corpuscles all remaining on the filter, the serum passing through colorless. This is due to the agglutination of the red cells, which are formed into masses and thus fail to pass through the pores of the filter. Fibrin does not seem to be formed in the process, as was at one time supposed, but the nature of the cementing substance is unknown. Stillmark supposed that ricin formed these masses of red cells in the blood-vessels, and that the symptoms were due to the emboli resulting, but this is certainly incorrect, for the blood of immune animals reacts in the same way, yet these are not poisoned by many times the usual fatal dose of ricin. Gunn has shown that ricin similarly agglutinates any suspended particles which, like the red cells, possess a negative charge and that this agglutination is accompanied by an abolition of the negative charge on the particles or red cells. He has suggested, therefore, that the agglutination of red cells by ricin may be, partly at least, non-specific and of the nature of the precipitation of one colloid by a colloid of opposite sign.

Ehrlich found that animals rapidly acquire immunity to the action of ricin, if they receive for some time small non-toxic doses. From this discovery has arisen the Ehrlich side-chain theory, which plays such an important rôle in medicine at the present time. By gradually increasing the daily amount of ricin, rabbits have attained an immunity of 5,000, that is, they are not affected by 5,000 times as much ricin as would have killed them had no preliminary treatment been instituted.

Ricin and its antitoxin are not used in therapeutics, but ricin has repeatedly given rise to poisoning, from the beans being taken as a substitute for the oil. Cattle have also been poisoned by being fed on the refuse of castor oil beans after the oil had been expressed.

Another vegetable toxin which resembles ricin very closely in its effects is **Abrine**, which is obtained from the seeds of Abrus precatorius or jequirity, the familiar scarlet and black beans, which are often formed into necklaces. Abrine contains two poisons, a globulin and an albumose, of which the former is the more powerful. It induces the same symptoms as ricin, but is less poisonous, and immunity can be acquired in the same way. Animals which are immune to ricin are not more resistant to the action of abrine than others, because the two poisons form different antitoxins.

Crotin is another toxin, which is found in the Croton Tiglium, but which does not pass into croton oil. It is less poisonous than ricin and abrine, but resembles them in most other points, except that it does not cause agglutination of the blood cells of certain animals, while ricin and abrine have this effect in all kinds of blood hitherto examined.

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CLASSIFICATION OF DRUGS ACCORDING TO THEIR THERAPEUTIC USES

I. Drugs applied for their local action to the skin, wounds, or visible mucous membranes.

Corrosives or caustics.

Nitric acid, 90
Silver nitrate, 134
Zinc chloride, 120
Chromic acid, 148
Alum, 122
Arsenic, 175
Trichloracetic acid, 91
Phenol, 778
Salicylic acid, 695
Iodine, 75
Carbon dioxide snow, 99

Irritants.

Chloroform, 291
Turpentine oil group, 202
Mustard, 203
Cantharides, 204
Camphor, 209
Menthol, 213
Iodine, 75
Ammonia, 58

Disinfectants and antiseptics.

Detergents, 777
Hydrogen peroxide, 790
Permanganate of potassium, 791
Phenol, 778
Mercuric salts, including organic mercury compounds, 785
Silver nitrate and organic silver compounds, 788
Boric acid, 792
Iodine, 796
Iodoform, 797
Cresol, 783
Hypochlorites, chloramine, and other chlorine derivatives, 799
Tar, 805
Salicylic acid, 785
Picric acid, 785
Alcohol, 778
Volatile oils (thymol, eucalyptol, etc.), 207
Antiseptic dyes, 800
Sulfonamides, 725
Antibiotics, 743

Disinfectant or irritant ointments in parasitic skin diseases.

Mercury ointments, 144
Sulfur ointment, 806
Tar, 805
Benzoin, styrax, and Peru balsam, 807
Naphthol, 804
Resorcin, 805
Pyrogallol, 802
Chrysarobin, 803
Pyrethrum, 814

Astringents.

Tannic acid series, 224
Iron preparations, 113
Bismuth preparations, 156
Zinc sulfate and oxide, 120
Copper sulfate, 117
Alum, 122
Alcohol, 265

Styptics.

Soluble astringents (see above).
Ferric chloride, 113
Alum, 122
Silver nitrate, 134

To contract vessels and reduce hemorrhage and swelling.

Epinephrine and substitutes, 485
Ephedrine, 497
Benzedrine, 500

Emollients or protectives.

Adeps, petrolatum, 193
Plasters and collodia, 196
Dusting-powders — starch, talc, chalk, iodoform, and many insoluble metallic powders, which may also be slightly astringent, 194

Local anodynes and analgesics for pain and itching.

Bicarbonate of potassium or sodium, 80
Cocaine, procaine, eucaine, Orthoform, etc., 404
Phenol, 778
Chlorbutanol, 314
Belladonna, 463
Some volatile oils (in dentistry).

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Local anesthetics.
Cocaine, procaine, etc., 404
Cold by evaporation of ethyl chloride, 421

Drugs administered internally to increase the secretion of perspiration (diaphoretics or sudorifics).
Pilocarpine, 459
Ipecacuanha, 720
Ipecacuanha and opium (Dover's powder), 720

Drugs administered internally to lessen secretion of perspiration.
Atropine and belladonna, 463

II. Drugs used for affections of the alimentary tract.

MOUTH AND THROAT.

Demulcents.
Liquorice, 191
Acacia, 193

Astringents.
Tannin group, 224
Iron, 113
Alum, 122

Antiseptics.
Boric acid, 792
Perborates, 793
Volatile oils, 208
Hydrogen peroxide, 790
Silver compounds, 788
Sulfonamides, 725
Antibiotics, 743

To lessen salivation.
Atropine, 463

Flavoring substances.
Sugars, 215
Volatile oils series, 207
Acids (citric), 92
Saccharin, 215

STOMACH.

Digestives.
Dilute hydrochloric acid, 90
Pepsin, 220
Pancreatin, 221

Emetics.
Apomorphine, 363
Ipecacuanha, 717
Sodium chloride, 43
Mustard, 203
Warm water.
Tartar emetic, 162
Copper sulfate, 117
Zinc sulfate, 119

To lessen irritation or vomiting.
Opium, 329
Chlorbutanol, 314
Bromides, 366
Lime-water, 63
Bismuth, 156
Cold (ice).
Carbon dioxide waters, 96
Demulcents, 191
Barbiturates, 316

To lessen acidity.
Sodium bicarbonate, 80
Magnesium oxide and carbonate, 65
Lime-water, 63
Calcium carbonate, 63
Bismuth subcarbonate, 156
Aluminum hydroxide, 122
Magnesium silicate, 65
Aluminum phosphate, 122

To increase secretion.
Simple bitters, 218
Nux vomica, 387
Cinchona, 697

Carminatives.
Volatile oils, 207
Alcoholic preparations, 266
Carbon dioxide waters, 96
Bicarbonates, 78
Camphor, 209
Charcoal, 227

INTESTINE

To promote digestion.
Pancreatin, 221

To promote evacuation—purgatives.
Mild aperients—castor oil, 231
Sulfur, 232
Phenolphthalein, 235
Agar-agar, 244
Liquid petrolatum, 232
Rhubarb and aloes group, 233
Saline purgatives, 239
Mercurial purgatives—calomel and metallic mercury preparations, 139
Glycerin suppositories, 232
Enemata.

In intestinal atony.
Pituitary extract, 531
Physostigmine, 451
Neostigmine, 456

To lessen movement.
Opium, 329
Tannic acid series, 224
Bismuth salts, 156
Atropine (to relax spasm), 463

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To destroy parasites—anthelmintics.

Male fern, 758
Santonin, 761
Pelletierine, 759
Carbon tetrachloride, 764
Ethylenetetrachloride, 766
Oil of chenopodium, 760
Hexylresorcinol, 766
Thymol, 760
Quassia enema, 219
Gentian violet, 767
Phenothiazine, 767
Ficin, 767

Antiseptics.

Mercurial purges—calomel, 142
Vegetable purgatives (castor oil), 231
Sulfonamides, 739

III. Drugs used for their effects on the circulation.

HEART.

To strengthen contraction.

Digitalis, 612
Strophanthin, 708

In auricular fibrillation and flutter

Digitalis, 612
Quinidine, 708

To accelerate pulse.

(Atropine, 463)
(Caffeine, 393)

To slow the pulse.

Digitalis, 612
Quinidine, 708
Mecholyl, 447

VESSELS.

To contract vessels or raise blood-pressure.

Epinephrine (intravenously or subcutaneously), 485
Ephedrine and substitutes, 497

To relax vessels and lower blood-pressure (angina pectoris).

Nitrites, 642
Theobromine and Theophylline preparations, 400
Papaverine, 349

To arrest internal hemorrhage.

Opium and morphine (to allay restlessness), 329
Ergot, 507

To remove fluid (dropsy, anasarca).

Digitalis, 612
Diuretics.
Theobromine, 401
Saline cathartics, 239
Merbaphen and Salyrgan (Mersalyl), 143

IV. Drugs used for their effects on the genito-urinary system.

To increase the flow of urine (diuretics).

Caffeine and theobromine, 393
Digitalis, 612
Saline diuretics, 53
Citrates, acetates, 53
Mercury—calomel, merbaphen, salyrgan (Mersalyl), 143
Water, 53
Urea, 53

To lessen the flow of urine in diabetes insipidus.

Pituitary preparations (subcutaneously or into nasal cavity), 531

To render the urine less acid.

Alkali bicarbonates, 78
Acetates, 83
Citrates, 83

To make the urine more acid.

Acid sodium phosphate, 66
Acids, 86
Ammonium chloride, 56
Mandelic acid, 809

To render the urine antiseptic.

Sulfonamides, 725
Methenamine, 808
Penicillin, 743
Mandelic acid, 809
Streptomycin, 751

Local antiseptics; silver compounds and potassium permanganate (applied locally), 771, 802
Sulfonamides, 725
Penicillin, 743

To promote contraction of the uterus (ecbolics).

Pituitary extract, 531
Ergot, 507
Quinine, 708
Castor oil, 231
Ergonovine, 515

To promote menstruation (emmenagogues).

Iron, 111
Aloes, 233
Estrogens, 564

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V. Drugs used for their effects on the respiratory system.

To stimulate the respiratory center.

Caffeine, 393
Atropine, 463
Strychnine, 379
Carbon dioxide, 5 to 10 per cent, 96
Picrotoxin, 389
Nikethamide, 392
Metrazol, 392
Cyanide, 663

To reduce the irritability of the center in cough.

Opium, morphine, and codeine, 329
Dihydromorphinone, 349

To increase and liquefy the bronchial secretion.

Ipecacuanha, 717
Tartar emetic, 161
Ammonium chloride, 56
Squills, 612
Ammonium carbonate, 56
Iodides of the alkalies, 70
Terpene hydrate, 207

To relax bronchial spasm in asthma.

Epinephrine, 485
Ephedrine, 497
Belladonna and atropine, 463
Nitrites, 642
Iodides, 70
Aminophylline, 400

Pulmonary antiseptics.

Sulfonamides, 725
Penicillin, 743

VI. Drugs used for their effects on the central nervous system.

Stimulants.

(*a*) *The spinal cord.*
Strychnine, 397

(*b*) *The brain and medulla oblongata.*
Caffeine, 393
Atropine, 463
Picrotoxin, 389
Metrazol, 392

Depressants.

(*a*) *General anesthetics.*
Ether, chloroform, ethyl chloride, nitrous oxide, ethylene, etc., 269

(*b*) *Hypnotics or narcotics.*
Opium and morphine, 329
Chloral group, 310
Barbituric acid series, 316
Bromides, 366
Scopolamine, 476
Isonipecaine, 358

(*c*) *In epilepsy.*
Bromides, 366
Phenobarbital, 316
Phenytoin, 373
Tridione, 377

Surgical anesthetics.

(*a*) Chloroform, ether, 269
Ethyl chloride, 291
Ethylene, 300
Nitrous oxide, 295
Cyclopropane, 303
Divinyl ether, 292
Pentothal sodium, 326
Tribromethanol, 305

(*b*) Barbituric acid series, 316

To relieve pain—analgesics or anodynes.

Opium, 329
Antipyretics, 673
Salicylates, 687
Neocinchophen, 669
Isonipecaine, 358

In headache.

Antipyretics, 673
Acetylsalicylic acid, 692
Caffeine, 393
Bromides, 366
Ergotamine (migraine), 507

VII. Drugs used to reduce fever temperature.

Antipyretics, 673
Quinine, 697
Salicylates, 687

In chills.

Alcohol, 252
Ipecacuanha and opium (Dover's powder), 720

VIII. Drugs used for their effects on the liver.

To increase the secretion of bile—cholagogues.

Bile salts, 222
Dehydrocholic acid, 223

For their lipotropic action.

Choline, 444, 601
Methionine, 821

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IX. Drugs used for their effects on the blood.

To increase the hemoglobin.
Iron, 107
Copper, 115

To increase the number of red blood cells in pernicious anemia.
Liver preparations, 573
Stomach preparations, 578
Folic acid, 601

To reduce leucocytosis and erythrocytosis.
Irradiated phosphorus, 152

To increase the acid.
Ammonium chloride, 56

To increase the alkali.
Alkali carbonate group, 78
Acetates, citrates, and lactates, 83

To increase coagulability.
Vitamin K, 610

To decrease coagulability.
Heparin, 580
Dicumarol, 581

X. Drugs used for specific diseases.

In malaria.
Quinine, 697
Quinacrine, 711
Pamaquine, 714
Chloroquin, 716

In pneumonia.
Sulfonamides, 725
Antipneumococcus serum, 818
Penicillin, 743

In syphilis.
Penicillin, 743
Mercury, 142
Bismuth, 154
Iodides, 70
Arsenicals, 177

In diphtheria.
Antidiphtheritic serum, 818
Penicillin (?), 743

In tetanus.
Antitetanic serum, 818
Morphine, 329
Barbiturates, 316
Chloral, 310
Magnesium intraspinally, 65

In cerebrospinal meningitis.
Antimeningococcus serum, 818
Sulfadiazine, 728
Penicillin, 743

In amebic dysentery.
Ipecacuanha, 717
Emetine, 720
Diodoquin, 724
Vioform, 724
Chiniofon, 724
Carbarsone, 722

In rheumatic fever.
Salicylates, 687

In thyroid diseases.
Thyroid extract, 540
Iodides, 70
Iodine, 70
Thiouracil, 548

In trypanosomiasis.
Arsenic, 177
Antimony, 160
Germanin, 185

In gout.
Colchicum, 666
Neocinchophen, 669

In hypoparathyroidism.
Parathyroid extract, 549
Dihydrotachysterol, 552
Calcium salts, 59

In adrenal cortical insufficiency.
Adrenal cortical extract, 553
Desoxycorticosterone, 554

In ovarian deficiencies.
Estrogens, 564
Progesterone, 570
Gonadotropins, 564

In gonorrhea.
Penicillin, 743

In rickets and osteomalacia.
Cod-liver oil (vitamin D), 606
Halibut liver oil, 607
Viosterol, 608

In diabetes mellitus.
Insulin, 558

In beri-beri.
Thiamin, 591

In ariboflavinosis.
Riboflavin, 593

In scurvy.
Vitamin C, 602

In pellagra.
Nicotinic acid and its amide, 595

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In leprosy.

Chaulmoogra oil, 650
Hydnocarpus oil and esters, 651
Promin, 651

XI. Drugs used locally for their effects on the eye.

Astringents, Section I.
Disinfectants, Section I.
Caustics, Section I.
Anodynes and anesthetics, Section I.

Drugs dilating the pupil and relaxing the accommodation—mydriatics.

Atropine, 463
Homatropine, 477
Scopolamine, 476
Cocaine, 404
Benzedrine sulfate, 500

Drugs contracting the pupil and the ciliary muscle—myotics.

Physostigmine, 451

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INDEX

A

ABORTIFACIENTS, lead salts as, 125
volatile oils as, 209
Abortion, following use of salicylates, 689
induced by volatile oils, 209
in lead poisoning, 126
threatened, use of progesterone in, 571
use of vitamin E in, 610
Abrine, 822, 823
use of, as irritant, 201
Abrus precatorius, 823
Absinthe, 210
oil of, 207
Absorption, of ammonium salts, 57
of iodides, 71
See also under specific drug
Acacia, 51, 192
Aceta, 37
Acetanilide, 673, 674
series, 673–687
Acetanilidum, 686
Acetarsol, 186
Acetarsone, 185, 722
Acetates, 83
Acetic acid, 90–91
Acetomenaphthonum, 805
Acetophenetidin, 686
Acetophenetidinum, 686
Acetum scillæ, 640
Acetylation, of sulfonamide drugs, 727
Acetyl-beta-methyl choline, 447–449
Acetycholine, 445–447
antagonism to atropine, 466
Acetylene, 293
Acetylhomocholine, 447
Acetylmorphine, 350
Acetylsalicylic acid, 686, 687, 688, 692–693, 695
Acetylsulfadiazine, 736
Acetylsulfamerazine, 736
Acetyl-sulfanilamide, 730, 732
use of, in urinary tract infections, 738
Acetylsulfapyridine, 736
Acetylsulfathiazole, 736
Acetyltannic acid, 226
Achylia gastrica, 89
Acid sodium phosphate, use of, with methenamine, 808
Acidosis, from ammonium salts, 58
diabetic, treatment of, 562
following use of sulfonamides, 727, 735
symptoms of, 88, 89
treatment of, 84
Acids, 86–92
See also under specific acids.
Acidum aceticum glaciale, 91
acetylsalicylicum, 695
ascorbicum, 605
Acidum benzoicum, 697
boricum, 794
hydrochloricum, 91
hydrocyanicum dilutum. 666
mandelicum, 809
nicotinicum, 597
nitricum, 90
salicylicum, 695
sulphuricum, 90
tannicum, 227
Acne, use of resorcin in, 805
Acocanthera, 612
Aconine, 653
Aconitine, 652–654
Aconitum, 654
ferox, 652
japonicum, 652
lycoctonum, 653
napellus, 652
Acridine, 801
dyes, as antiseptics, 801
Acriflavina, 802
Acriflavine, 801
Acri-violet, 774
Acromegaly, 528
Actinomyces antibioticus, 753
lavendulæ, 753
griseus, 751
Actinomycin A, 753
Actinomycosis, 738, 746
use of iodides in, 74
Adalin, 373
Adams-Stokes syndrome, use of barium in, 64
use of paredrine in, 505
Addison's disease, 55
treatment of, 556–557
Adeps, 194
benzoinatus, 195
lanæ, 195
hydrosus, 195
Adhesive plaster, 196
Administration, methods of, of drugs, 29
Adonis vernalis, 612
Adrenal cortex, 553–558
extracts of, 553–558
action of, 554–555
chemistry of, 553–554
therapeutic use of, 556–557
cortical extracts. *See* Adrenal Cortex.
medulla, 557
Adrenalin. *See* Epinephrine.
Adrenaline. *See* Epinephrine.
Adrenergic action, 494
Adrenine, 485
Adrenogenital syndrome, 556
Adrenotrophic hormone, of pituitary, 529
Aërobacter aerogenes, 753
Aerosols, 813

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Æther, 293
Æthylenum, 302
Æthylis aminobenzoas, 422
chaulmoogras, 651
chloridum, 294
oxidum, 294
Æthylmorphinæ, 355
Affinity, elective, of drugs, 18
Agar, as laxative, 244
Agaricin, 479
Agaricus albus, 479
muscarius, 440
Age, effect of, on drug action, 25
Aglucones, of digitalis, 613
Agranulocytosis, 676–677
Agrostemma, 657
githago, 656
Ague, brassfounders', 119
See also Malaria.
Albaspidinin, 758
Albucid, 730
Albumin, human blood, 820
beef blood, 820
Alcohol, 252–268
absolute, 268
amyl, 268
butyl, 268
ethyl. *See also* Ethyl.
methyl, 267–268
propyl, 268
use of, as disinfectant, 778
wood, 267–268
Alcoholic preparations, 37
Alcoholics, use of salicylate in, 688
Alcoholism, chronic, 264
treatment of, 265
Aldarsone, 184
Algæ, action of copper on, 117
Alimentary tract, action of anesthetics on, 280
of opium derivatives on, 338
of volatile oils on, 208
drugs and, 30
Alkali disease, 151
Alkalies, 78–83
antidotes for, 90
hydrates and carbonates of fixed, 78
poisoning from, 82
salts of, 53–59, 78–83
use of, in diabetes, 84
Alkaline earths, salts of, 59
reserve, 89
Alkaloids, 33
Alkalosis, 82
from sodium bicarbonate, 81
Alkasal, 122
Alkyl chlorides, use of, as disinfectants, 778
Allergy, to iodine, 77
rôle of histamine in, 519–520
Allicin, 755
Alloxan, 563
Allyl-isosulphocyanate, 203
Almond oil, 195
Almonds, bitter, poisoning by, 663
Aloes, 234, 245
preparations of, 245
Aloin, 234
Alpha-naphthol, 804
Alsol, 122
Alum, 121–122
Aluminum, hydroxide, as antacid, 81
salts of, 121–123
uses of, 122
silicate, as dusting powder, 194
Alumnol, 122
Alupin hydrochloride, 415
Alurate, 318
Amanita muscaria, 440
Amblyopia, in chronic alcoholism, 264
lead, 128
tobacco, 439
Ameba, action of emetine on, 719
Amebiasis, 719–721
use of carbarsone in, 722
of emetine in, 720–721
of quinoline derivatives in, 724
Amidopyrina, 687
Amidopyrine, 673
Aminoacridine, 801
Aminobenzene sulfonamide, 726, 742
Aminobenzoic acid, 600
Amino-oxidase, 594
Aminophylline, 400–402
Aminopyrina, 686
Aminopyrine, 673
Aminoquin naphthoate, 716
Ammonia, 85–86
excretion of, 88–89
spirits of, 59
substituted, 58
Ammonii bicarbonas, 86
carbonas, 86
Ammonium, 56
acetate, as diuretic, 53
benzoate, 697
bicarbonate, 86
carbonate, 85–86
chloride, as diuretic, 52
preparations of, 59
therapeutic uses of, 58
use of, with methenamine, 808
citrate, as diuretic, 53
derivatives of alkaloids, 427
ichthosulphonate, 806
mandelate, 809
salts of, 56–59
therapeutic uses of, 58
Amoeba, effect of quinine on, 698
Amphetamine, 500–502
sulfate, 500
therapeutic uses of, 501
Amydricaine, 415
Amygdalæ, oleum, 195
Amygdalin, 216, 663
Amyl alcohol, 268
Amyl nitrite, 642–650
action of, 643–647
excretion of, 646
pearls of, 646
use of, in lead colic, 126
Amylcaine, 415
Amylene hydrate, 314
Amyleni hydras, 315

Bharatiya Vidya Bhavan, New Delhi Collection

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Amylis nitris, 649
Amylsine hydrochloride, 415
Amylum, 193
Amytal, 318, 328
Anabasine, 429
Anabasis aphylla, 429
Anæsthesia. *See* Anesthesia.
Anæsthesine, 422
Anæsthetics. *See* Anesthetics.
Anagallis, 221
Anagrine, 429
Anagyris fœtida, 429
Analeptic, 389–392
  use of camphor as, 212
Analgen, 673
Analgesics, antipyretics as, 686
  isonipecaine as, 358–361
  morphine as, 351
  opium as, 351
Anaphylaxis, rôle of histamine in, 519–520
Anayodin, 723, 724
Ancylostoma duodenale, 757
Ancylostomiasis, 757, 760
Andira araroba, 803
Androgens, 571–573
Androsterone, 571
Anemia, Cooley's, 111
  due to cobalt deficiency, 149
  hemolytic, following sulfonamide therapy, 735
  hypochromic, 112
  in lead poisoning, 125
  Mediterranean, 111
  nutritional, 602
  use of copper in, 111, 117
  use of iron in, 111
Anesthesia, 307
  apparatus for administering, 287
  caudal, 421
  by cold, 202
  dangers of, 285
  gas machine for, 298
  infiltration, 419
  local by venous injection, 419
    See also Local anesthetics.
  by magnesium salts, 65
  by physical methods, 421
  practical aspects of, 289, 299
  premedication in, 307
  principles of, 287
  by refrigeration, 421
  regional, 419
  signs of, 271
  spinal, 419
  surface, 417
  terminal, 418
  use of barbiturates in, 326
    morphine in, 353
    oxygen in, 94
Anesthesin, 415
Anesthesine, 422
Anesthetics, avertin as, 305–306
  chemistry of, 251
  choice of, 284
  comparison of, 308
  cyclopropane as, 303
  deaths from, 285
Anesthetics, ethylene as, 300
  general, 269–310
  local, 404–423
    chemistry of, 412
  nitrous oxide as, 295
  therapeutic uses of, 290
Aneurin, 593
Aneurinæ hydrochloridum, 593
Angina, agranulocytic, 676
  pectoris, use of nitrites in, 648
    use of xanthines in, 401
Angioneurotic edema, 62
Anhydro-oxyprogesterone, 570
Anhydrotics, tellurates as, 151
Aniline, 673
Anions, miscellaneous, 66
Anise, 216
Anoxia, 93–94
Antacids, 81
  aluminum salts as, 121
Antagonism, in drug action, 28
Anterior pituitary lobe, 527
Anthelmintics, 757–769
  papain as, 222
Anthiomaline, 163
Anthracene, 233
  purgatives, 233
Anthraquinone, 233
Anthrax, 746, 747
Antiamebic drugs, 717–725
Antianthrax serum, 819
Antiarin, 616
Antiaris, 616
  toxicaria, 612, 616
Antibiotics, 743–756
Antibodies, 816
  preparation of, 818
Anticoagulants, 84, 580–581
Anticonvulsants, 373–379
Anti-dermatitic vitamin, 597
Antidiuretic, posterior-pituitary liquid as 537
Antidysentery serum, 41, 819
Antierysipelas serum, 819
Antierysipeloid serum, 819
Antifebrine, 673, 686
Antihydrotic, agaricin as, 479
Antimalarials, 697–717
Antimeningococcus serum, 819
Antimony chloride, 160
  compounds of, 160–165
    organic, 162–165
    pentavalent, 164
    toxicology of, 160
    trivalent, 163–164
  potassium tartrate, 160
  preparations of, 165
  sodium tartrate, 165
  sodium thioglycollate, 162–163
Antinosine, 798
Antipneumococcic serum, type specific, 819
Antipyretics, 673–687
  action of, 677–683
  chemistry of, 673
  preparations of, 686–687
  site of action of, 677

Bharatiya Vidya Bhavan, New Delhi Collection

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Antipyretics. symptoms of, 674
therapeutic use of, 683–686
toxicity of, 676
Antipyrina, 686
Antipyrine, 673
action of, 676
series, 673–687
Antirachitic vitamin, 41, 605–609
Antisepsis, 771
Antiseptics, 771–814
alcohols as, 263
aluminum salts as, 121–122
intestinal, use of sulfonamides as, 729–730
mercury as, 138
See also under specific drugs.
Anti-snake biter serum, 819
Anti-sterility vitamin, 609
Antitoxins, 818–820
standardization of, 41
See also under specific drugs.
Antitoxinum diphthericum, 819
Œdematiens, 819
Scarlatinæ streptococcicum, 819
Staphylococcicum, 820
Tetanicum, 819, 820
Vibrio septicum, 820
Welchicum, 820
Antivenin antitoxin, 819
Anuria, in mercury poisoning, 136, 140
Apalache tea, 394
Aperients, mild, 231–233
preparations of, 244
sugar as, 214
Aphrodisiac, alcohol as, 263
cantharidin as, 204
use of yohimbine as, 659
Aphthæ, use of boracic acid in, 793
potassium chlorate in, 796
Apoatropine, 464
Apocodeine, 364
Apocynum cannabinum, 612
Apomorphine, 363–365
use of, in alcoholism, 265
Apothesine, 415
Aqua tofana, 165
Aquæ, 36, 217–218
Aqueous preparations, 36
Arabin, 193
Arabinic acid, 193
Aralen, 716
Arbutin, 403
Arctostaphylos uva ursi, 403
Areca catechu, 462, 764
nut, 764
Arecoline, 462, 764
Argenti nitras, 134
Argentoproteinum, 790
Argentum proteinicum forte, 790
mite, 790
Arginine, 616
Argyn, 789
Argyria, 132–133, 789
Ariboflavinosis, 594
Aristol, 798
Aromatic elixir, 268
Aromatics, 771
Arrow poisons, 612, 616
Arsenic, 165–187
acid, 166
eaters, 173
excretion of, 174
metallic, 166
organic compounds of, 177–186
toxicology of, 178
poisoning by, acute, 166, 176
chronic, 167
symptoms of, 167
treatment of, 176
preparations of, inorganic, 165–177
therapeutic uses of, 175–176
sulfide, 165, 174
therapeutic use of, 175–176
tolerance to, 173
toxicology, 167–174
trioxide, 166, 176
use of, in syphilis, 179–187
white, 176
Arsenious acid, 166, 177
use of, as caustic, 175
Arseniuretted hydrogen, 174
Arsenobenzol, 180
Arsenosophenyl butyric acid, 186
Arsenophenylglycin, 180
Arsenoxide, 179
Arsine, 174
derivatives of, 206
Arsphenamina, 186
Arsphenamine, 40, 179–182, 186
mechanism of action of, 179
toxicity tests of, 40
Artemisia pauciflora, 761
Artemisin, 761
Arterenol, 506
Arterio-sclerosis, use of digitalis in, 635
Arthralgia, lead, 127
Arthritis, rheumatoid, 738
use of gold in, 147
Asafetida, oil of, 213
Asagræa officinalis, 654
Ascariasis, 757, 766
use of hexyresorcinol in, 767
Ascaridol, 760
Ascaris, 766
lumbricoides, 757, 760, 763
Ascorbic acid, 602–605
chemistry of, 602–603
occurrence of, 603
pathology of, 604
preparations of, 605
therapeutic use of, 604–605
Asepsis, 771
Aspergillic acid, 754
Aspergillus clavatus, 754
flavus, 754
Asphyxia, from carbon dioxide, 97
use of carbon dioxide in, 98
Aspidinin, 758
Aspidinol, 758
Aspidium athamanticum, 758
filix-mas, 758
oleoresin of, 757, 758–759
preparations of, 768
spinulosum, 758

Bharatiya Vidya Bhavan, New Delhi Collection

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Aspidosamine, 659
Aspidosperma, 659
quebracho, 659
Aspidospermatine, 659
Aspidospermine, 659
Aspirin, 687-688
Assay, of penicillin, 745
Asthma, use of amyl nitrite in, 649
diphenylhydantoin in, 377
helium in, 100
oxygen in, 94
xanthines in, 401-402
Astringents, aluminum salts as, 121
bismuth salts as, 157
copper salts as, 117
heavy metals as, 103
tannic acid as, 226
zinc salts as, 119
vegetable, 224-227
A.T. 10, 552
Atabrine. *See* Quinacrine.
Atebrin musonat, 714
Atebrine, 711
Atophan. *See* Cinchophen.
Atoxyl, 178
Atropa belladonna, 463
Atropamine, 464
Atropine, 463-476
as antagonist, to muscarine, 442
to physostigmine, 453
to pilocarpine, 460
as antidote, to aconitine, 653
to epinephrine, 493
to mecholyl, 449
chemistry of, 463
detection of poisoning by, 449
preparations of, 484
symptoms of, 465-474
therapeutic uses of, 479-482
tolerance to, 475
use of, in anesthesia, 309
Atroscine, 463
Attar of roses, 207
Aurantiaceæ, 207
Aurantii amari cortex, 216
Auricular fibrillation, 710
use of digitalis in, 632
use of quinidine in, 709
flutter, use of quinidine in, 709, 710
tachycardia, use of quinidine in, 710
Avertin, 305-306
Avidin, 599
Azobenzene disulfonic acid, 800
Azochloramid, 799
Azo dyes, use of, as antiseptics, 800-801

B

Bacillary infection, of intestine, 729
Bacillus brevis, 753
paratyphosus A, 817
paratyphosus B, 817
typhosus, 817
Bacitracin, 753
Baking soda. *See* Sodium bicarbonate.
Bal, 176
Balantidiasis, use of carbarsone in, 723
Balsam, 34, 771
as antiseptic, 807
of Peru, 807
of Tolu, 697
Balsamum Peruvianum, 807
Tolutanum, 807
Barbaloin, 233
Barbital, 318
Barbitone, 327
Barbiturates, 316-327
antagonism of, 322-323
comparison of, 318-320
dose of, 318-321, 325
excretion of, 321-322
pharmacological action of, 316-321
poisoning by, 323
picrotoxin as antidote in, 391
treatment of, 324
preparations of, 327-328
synergism of, 322-323
Barbituric acid, derivatives of. *See* Barbiturates.
Barium, 64
antagonism of, by magnesium, 65
sulphate, 64
Barley, 193
water, 192
Basedow's disease. *See* Graves' disease.
Baths, therapeutic value of, 46, 49, 50
"Bayer 205," 185
Bearberry, 403
Beer, 268
Beerwort, 599
Belladonna, 463-476
poisoning by, treatment of, 482
preparations of, 483-484
therapeutic uses of, 479-482
Belladonnine, 464
Benadryl, 521
Benzaconine, 653
Benzamine, 414
Benzedrine, 500-501
sulfate, 500
Benzene, 662-663
Benzestrol, 566
Benzoates, 696-697
Benzocaine, 422
Benzoic acid, 696-697
Benzoin, 697
compound tincture of, 807
Benzoinum, 807
Benzol, 662-663
Benzoyl-ecgonine, 405
Benzyl alcohol, 415
benzoate, 697
bromide, 206
iodide, 206
Benzylis benzoas, 697
Berberine, 218, 657
Bergamot, 217
Beriberi, 591-592
Beryllium, 151
Betaeucaine, 414
Beta-naphthol, 804-805
Betel nut, 462
Betula lenta, 687

Bharatiya Vidya Bhavan, New Delhi Collection

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Bhang, 361
Bichloride, of mercury, 785
Bichromate, of potassium, 148
Biebrich scarlet, 800
Bile, 222
secretion of, effect of mercury on, 140
effect of salicylates on, 691
salts, 222–224
use of, with vitamin K, 611
Bilharziasis, 163
Biochemistry, rôle of, in pharmacology, 13
Biological assay, 38
preparations in B. P. requiring, 40
in U. S. P. requiring, 39
Biologicals, 815–823
Bios, 599
Biotin, 599–600
Birch bark, 687
Bismarsen, 183
Bismo-cymol, 158
Bismosol, 158
Bismuth, 154–159
ethylcamphorate, 158
preparations of, 159
salts of, 154–161
action of, 156
local action of, 155
therapeutic use of, 156
toxicity of, 154–156
sodium tartrate, 158
subcarbonate, 157, 159
as antacid, 81
subnitrate, 157, 159, 642
basic, 789
subsalicylate, 158
tribromphenate, 789
use of, in syphilis, 157–159
Bismuthi et potassi tartras, 159
salicylatis, 159
subcarbonas, 159
subnitras, 159
Bitter almonds, 216
orange peel, 216
Bitters, simple, 218
use of quinine as, 701
Bittersweet, 657
Black draught, 245
Black-tongue, 595
Black-water fever, 702
use of quinacrine in, 713
Bladder, effect of morphine on, 341
Blastomyces, 746
dermatitis, 754
Blaud's pills, 113
Blazing-star, 656
Blind staggers, 151
Blindness, following use, of male fern, 759
of pelletierine, 759
of salicylates, 690
Blood, acids in, 88
action of arsenic on, 172
action of bile salts on, 223
alcohol content of, 255
bromide content of, 370
chloroform content of, in anesthesia, 280
Blood, effect of cathartics on, 241
effect of mercury on, 141
effect of quinine on, 702
effect of saponins on, 657
effect of toxalbumins on, 823
ether content of, in anesthesia, 280
human, derivatives of, 820
lead content of, 126
poisons affecting, 661–663
solubility of nitrous oxide in, 298
Blood-cells, stippled, 125
Blood pressure, effect of alcohol on, 257
of ammonium salts on, 56
of anesthetics on, 275
of camphor on, 211
of digitalis on, 623
of ether on, 275
of nitrites on, 644, 649
of salicylates on, 690
Blood-serum, human, 820
Blood vessels, effect of anesthetics on, 278
of digitalis on, 623
Blue mass, 146
ointment, 146
pill, 146
Blumea balsamifera, 210
Body fluids, exchange of, 44
osmotic pressure of, 45
Bone, fluorides in, 68
in phosphorus poisoning, 189
Bone-marrow, effect of cobalt on, 149
Boracic acid, 792–794
Boral, 122
Borax, 792–794
Boric acid, 792–794
Borneocamphor, 210
Borneol, 210, 212
Botulism antitoxin, 819
Bougies, 29
Bowel. *See* Intestine.
B. Prodigiosus, 746
Brandy, 268
"Brassfounders' ague," 119
Brassica nigra, 203
sinapoides, 203
Brayero, 758
anthelmintica, 758
Bright's disease, 55
Brilliant green, 802
British Anti-Lewisite, 176
Pharmaceutical Codex, 35
Bromacetone, 206
Bromates, as oxidizing disinfectants, 795
Brombenzyl cyanide, 206
Bromelin, 221
Bromethol, 307
Brometone, 372–373
Bromides, 366–373
distribution and excretion of, 367–368
eruptions following use of, 370
poisoning from, 369
treatment of, 371
symptoms from, 366–367
therapeutic use of, 371
with quinine, 706
Bromine, as disinfectant, 812
Bromism, 368–369

Bharatiya Vidya Bhavan, New Delhi Collection

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Brommethylethylketone, 206
Bromsulfalein, 235
Bromural, 373
Bronchi, action of epinephrine on, 491
Bronchiectasis, use of oxygen in, 94
Bronchitis, 70
use of oxygen in, 94
Broom plant, 428
Broom-Clark method, 516
Brucellosis, 738
use of sulfonamides in, 737
of streptomycin in, 752
Brucine, 379, 387
Buchu, 403
Bufagin, 616
Bufo agua, 616
vulgaris, 616
Bufotalin, 616
Bufotoxin, 616
Bulbocapnine, 365–366
Burbot liver oil, 586
Burnett's solution, 120
Burns, 557
acid, 87
use of tannic acid in, 226
Butacaine, 413–414
Butamin, 415
Butesin, 415
Butter-yellow, 600
Butyl alcohol, 268
aminobenzoate, 415
chloral hydrate, 314
Butyn, 414
Butyrylcholine, 447
Buxine, 218

C

Cacao, 394, 402
butter, 196
Cachets, 38
Cachexia thyreopriva, 541
Cacodylates, 178
Cadmium, 149
Cæsium, salts of, 55
Caffeine, 394–402
preparations of, 403
therapeutic use of, 400
in alcoholic intoxication, 265
Cajuputi spiritus, 217
Calabar bean, 451
Calabash curare, 423
Calabrine, 451
Calamine, 120
Calciferol, 606, 608
Calcii chloridum, 63
gluconas, 63
hydroxidum, 63
iodobehenas, 77
lactas, 63
Calcium, 59–64
blood, effect of parathyroid extract on, 550
in rickets, 605
carbonate, 63
use of, as antacid, 81
as dusting powder, 194
Calcium, chloride, preparations of, 62, 63
use of, in lead colic, 130
deficiency of, 60
effect of desiccated thyroid on metabolism of, 544
gluconate, 62
hydrate, 62
hydroxide, 62
metabolism of, in rickets, 605
oxide, 62
relation of, to vitamin D, 60
requirements of, for adult, 60
in pregnancy, 60
rôle of, in body, 59
in blood, 60
salts, 59–64
absorption of, 59
action of, 59
preparations of, 63–64
therapeutic use of, 61
use of, in hypoparathyroidism, 552
Cali nuts, 451
Calomel, effect of, on kidney, 140, 142
ointment of, use in syphilis, 142
use of, as purgative, 140, 142
Calumba, 219
Calumbin, 218
Camphor, 209–213, 389
bromated, 212
local action of, 210
preparations of, 213
therapeutic use of, 212
Camphorated tincture of opium, 355
Camphorol, 212
Canadian hemp, 612
Canadine, 218, 657
Canavalin, 755
Cancer, use of avidin in, 600
use of radium in, 152
Cane sugar, 214
Cannabinol, 362
Cannabis, 361–362
Canquoin's paste, 120
Cantharidin, 204–205
Cantharis vesicatoria, 204
Capsaicin, 220
Capsicum, 220
Capsulæ diethylstilbestrolis, 569
Capxanthin, 585
Caraway, 216
Carbachol, 449–450
Carbacholum, 449–450
Carbaminoylcholine, 449–450
Carbarsone, 185, 722–723
toxic effects of, 723
Carbo activatus, 227
Carbohydrate, metabolism of, in anesthesia, 283
Carbolic acid, use of, as disinfectant, 778–782
Carbon, activated, 227
dioxide, 96–99
combining power, 58, 81
preparations of, 99
therapeutic uses of, 98
toxicity of, 97
use of, in alcoholic intoxication, 265

Bharatiya Vidya Bhavan, New Delhi Collection

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Carbon monoxide, 99-100
poisoning by, 94
tetrachloride, as anthelmintic, 764-766
preparations of, 768
toxicity of, 765
Carbonate, of ammonia, 86
of lime, 63
of magnesium, 83, 246
Carbonei tetrachloridum, 768
Carbonic acid. *See* Carbon dioxide.
Carbromalum, 373
Carbylamines, 664
Cardamomum, 216
Cardamon, 216
Cardiac output, effect of alcohol on, 257
effect of digitalis on, 626
effect of nitrites on, 644
effect of water on, 47
use of acetylene in determining, 293
Cardiazol, 392
Cardol, 206
Cargentos, 789
Carminative, camphor as, 210
chloroform as, 291
volatile oils as, 208
Carotenase, 585
Carotene, 585
international standard of, 588
Carrageenin, 193
Carragheen, 193
Carrion's disease, 164
Carron oil, 63
Carum, 216
Caryophyllum, 216
Casca bark, 612
Cascara sagrada, 234
preparations of, 245
Cassia, 214
cutifolia 245
angustifolia, 245
Castile soap, 196
Castor oil, 231-232
iodinated, 76
use of, with anthelmintics, 761
Castrate, effect of estrogens on, 567
Catalepsy, from bulbocapnine, 365
Cataplasma, 38
kaolini, 197
Cataplasmata, 38
Cataract, of eye, induced by dinitrophenol, 660
Catechu, 226
Cathartics, 228-247
hydragogue, 236
references to, 247
saline, 239-244
See also under specific drugs.
Caustic, arsenic as, 175
chromium as, 148
citrine as, 144
potash, 83
silver salts as, 134
zinc chloride as, 120
Central nervous system, action of ammonium salts on, 56
of anesthetics on, 272
of arsenic on, 170
Central nervous system, action of barbiturates on, 316
of camphor on, 211
of hypnotics on, 311
of sedatives on, 311
depressants of, 249
effect of digitalis on, 617-618
of heavy metals on, 106
of morphine on, 331-334
of nitrites on, 645
of phenol on, 780
of quinine on, 700-701
of salicylates on, 690-691
stimulants of, 379-404
See also under Specific drugs.
Cephæline, 717, 720
Cephælis acuminata, 721
ipecacuanha, 717, 721
Cephaline, 717, 720
Cera, 195
Cerata, 38
Cerates, 38
Cerebrospinal fluid, effect of alcohol on, 256
Cerebrum, effect of quinine on, 701
Cerium, salts of, 152
Cestodes, 758
Cetaceum, 195
Cevadilla, 654
seed, 654
Cevadilline, 654
Cevadine, 654
Cevitamic acid, 602-605
Chætomin, 755
Chalk, aromatic powder of, 63, 356
mixture, 63-64
prepared, 63
Chamælirium luteum, 656
Chamomile, 216
Champagne, 268
Chancroid, 738
Charas, 361
Charcoal, 227-228
Chaulmoogra oil, 650-651
Chaulmoogric acid, 650-651
Cheilosis, 594
Cheiranthus, 612
Chemotherapy, Ehrlich's views of, 179
principles of, 22 23
Chenopodiaciæ, 429
Chenopodium ambroisoides anthelminticum, 760
oil of, 757, 760
preparations of, 768
Cheyne-Stokes respiration, use of carbon dioxide in, 98
Chiniofon, 723-725
powder, 724
Chiniofonum, 725
Chloracetone, 206
Chloracetophenone, 206
Chloral, 310-312
dose of, 325
fate of, in tissues, 312
group of drugs, 310
hydrate, use of, in alcoholism, 265
local action of, 312

Bharatiya Vidya Bhavan, New Delhi Collection

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Chloral. symptoms from, 310–311
Chloralis hydras, 315
Chloralose, 314
Chloramina, 800
Chloramina-T, 799
Chloramine-T, 799
Chloramines, 799
Chlorate, of potash, 794–796
Chlorbutol, 314–315
Chlorella vulgaris, 755
Chlorellin, 755
Chloretone, 314
Chloride, excretion of, in fever, 49
See also Sodium chloride.
Chlorine, preparations of, as antiseptics, 799–800
use of, as disinfectant, 799–800, 812
as war gas, 206
Chloroazodin, 799
Chlorobutanol, 314
Chlorocresol, 784
Chloroform, action of, 272
effect of, on blood, 279
on blood vessels, 278
on heart, 277
on pupil, 280
on respiration, 273
excretion of, 283
preparations of, 294
references to, 294–295
symptoms of, 270
use of, as anesthetic, 269–310
Chloroformum, 294
Chlorohydroxytoluene, 784
Chloroquine, 716–717
Chlorosis, 111
Chloroxylenol, 784
Chloroxylon, 205
Chlorpicrin, 206
Chocolate, 394, 402
Cholagogues, 222, 230
magnesium sulfate as, 66
Choleretic, bile salts as, 222
Cholesterol, 606
Choline, 444–445, 601
ethers of, 447
Cholinesterase, 445
Chomane, 609
Chondrus, 193
Chorionic gonadotrophin, 564
Christmas rose, 612
Chromic acid, 148
Chromium, 148
poisoning by, 148
trioxide, 148
Chromosomes, effect of colchicine on, 668
Chrysanthemum cinerariæ folium, 814
Chrysarobin, 803
Chrysarobinum, 804
Chrysophanic acid, 233, 803
Chrysophanol, 234
Churrus, 361
Cicuta virosa, 389
Cicutoxin, 389
Cinchona, 697, 707
bark, 697
succiruba, 706
Cinchonamine, 704
Cinchonidine, 697, 698, 704, 706
Cinchonine, 697, 698, 704, 706
Cinchophen, 669–672
Cinchophenum, 672
Cineol, 761
Cinnamic acid, 697
Cinnamon, 216
Cinnamomum, 216
Cinnamyl-cocaine, 405
Circulation, effect of aconitine on, 653
of alcohol on, 256
of anesthetics on, 275
of arsenic on, 170
of atropin on, 474
of barbiturates on, 317
of caffeine on, 397
of epinephrine on, 486–490
of ergot alkaloids on, 512
of heavy metals on, 106
of histamine on, 521–522
of morphine on, 336
of nitrites on, 643
of nitrous oxide on, 298
of posterior pituitary extract on, 532–533
of salicylates on, 690
Circulation-time, 223
Cirrhosis, of liver, alcohol in etiology of, 261
use of choline in, 445, 601
Citrates, 83
Citric acid, 92
Citricin, 754
Citrine ointment, 144
Citrinin, 754
Citrophen, 674
Citryl phenetidine, 674
Claret, 268
Clavacin, 754
Claviceps purpurea, 507
Clonorchiasis, use of gentian violet in, 767
Clorarsen, 185
Clostridia infection, 738
welchii, 746
Clothing, disinfection of, 777, 810
Cloves, 216
Clysmata, 38
Clysters, 38
Coagulants, 582
Coagulation, of blood, rôle of calcium in, 61
Cobalt, 149
Cobefrine, 506
Cobra venom, 361, 427
Cocaine, 404–423
effect of, on eye, 417
habituation to, 408
local action of, 408–410
poisoning by, 411
symptoms from, 405
Cocainism, 408
Cocarboxylase, 592
Coccidiomycosis, 822
Cocculus indicus, 389
Cochineal, 215
Cochlea, effect of quinine on, 701

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Cocoa, 394, 402
Codamine, 329
Codeine, 330, 332-334
addiction to, 348
dose of, 351
preparations of, 355
therapeutic use of, 351-355
use of, as analgesic, 351
Cod-liver oil, 586
assay of, 40
preparations of, 589
use of, in rickets, 606, 608
vitamin D in, 605
Co-enzyme II, 596
Coffee, 394, 402
Coffeon, 402
Cola nut, 394
Colchiceine, 666
Colchici cormus, 669
semen, 669
Colchicina, 669
Colchicine, 666-669
Colchicum, 666-669
autumnale, 666
preparations of, 669
symptoms following use of, 666
therapeutic use of, 669
Cold, for local anesthesia, 202
bath, treatment by, in fever, 685
cream, 195
sponge, treatment by, in fever, 685
Coleoptera, 204
Colic, 62
lead, 126
Colica pictonum, 126
saturnina, 126
Colitis, from mercury poisoning, 136
Collargol, 789
Collodia, 37, 196
Collodion, 197
Collodium, 197
flexile, 197
Colloids, as demulcents, 191-192
protective action of, 773
Colocynth, 236
Colocynthein, 236
Colocynthin, 236
Columbin, 219
Columbo, 219
Common-ion-transfer, 33, 448
Compound acetanilide powder, 686
Concretio cordis, 637
Conditions, modifying the effects of drugs, 23
Condyloma, use of podophyllum in, 237
Condy's fluid, 792
Confectiones, 37
Confections, 37
Conhydrine, 428
Coniferæ, 202, 207
Coniine, 428
Conium maculatum, 428
Convallaria majalis, 612
Convolvulin, 236
Convulsant, cinchonidine as, 704
cinchonamine as, 704
insulin as, 562
Convulsant, metrazol as, 392
picrotoxin as, 389
use of, in psychiatry, 392
Convulsions, induced by camphor, 211
by ether, 286
by insulin, 559
by magnesium salts in, 65
by strychnine, 380-381
Convulsive. *See* Convulsant.
Copaiba, oil of, 207
Copavin, 353
Copper arsenite, 166
chloride, 117
chronic poisoning by, 116
salts of, 115-118
absorption of, 116
therapeutic use of, 117
toxicology of, 116, 118
sulfate, use of, in phosphorus poisoning, 190
Coramine, 392-393
Coriamyrtin, 389
Coriander, 216
Coriaria, 389
Corn-cockle, 656
Corn-salves, 695
Coronary occlusion, use of morphine in, 354
Coronilla, 612
Corrosives, acds as, 87, 90
alcohol as, 253
arsenic as, 171
copper as, 117
heavy metals as, 102
sublimate, 145
use of, as antiseptic, 785-786
Cortin, 553, 554
Corydalis cava, 365
Corynanthe yohimbi, 659
Cotarnine, 658
Cotton-seed oil, 195
Cough, use of opiates in, 352
use of squill in, 636
Counter-irritants, mechanism of action of, 199-200
Counter-irritation, 197-198
Countess of Cinchon, 698
Cowpox, 815
Cozymase, 596
Ceatine, excretion of, in vitamin E deficiency, 610
Credé's method, 134
Creolin, 783
Creosols, 805
Cresatin, 784
Cresols, 783-784
Cresotinic acid, 693
Cresylic acids, 783-784
Cretinism, 546
treatment of, 547
Crotalus antitoxin, 819
Crotin, 822, 823
Croton oil, as pustulant, 198
tiglium, 823
Cruciferæ, 207
Cryptopine, 329
Cryptorchidism, 564

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Cryptoxanthin, 585
Crystal violet, 767, 802
Cubebs, oil of, 207
Cupping, 202
Cupreine, 704
Cupri sulfas, 118
Curare, 423-427
as antagonist to physostigmine, 452
therapeutic use of, 426
use of, in anesthesia, 309
Curd soap, 196
Curine, 423
Currier's sumach, 389
Cusso, 758
Cutol, 122
Cyanide, poisoning by, 665
treatment of, 665-666
use of clinically, 666
Cyanmethemoglobin, 666
Cyanogen, 663
Cyanosis, following sulfonamide therapy, 735
following use of acetanilid, 675
Cyclamen europeum, 656
Cyclopropane, 303-304
Cyclopropanum, 304
Cymarin, 615
Cymarose, 614
Cynoctonine, 653
Cyrethylene, 293
Cystitis, 82
use of methenamine in, 808
use of silver salts in, 134
Cytisine, 429
Cytisus laburnum, 429
scoparius, 428, 429
Cytochrome, 107

D

Dakin's solution, 799-800
Datura, 464
stramonium, 463
DDT, 814
Deacetyldigilanids, 615
Dead tongue, 389
Deafness, from use of chenopodium, 760
Death camas, 654
Decocta, 36
Decoctions, 36
Dehydroandrosterone, 571
Dehydroascorbic acid, 603
Dehydrocholesterol, 606
Dehydrocholic acid, 223
Dehydrositosterol, 607
Delirium tremens, 264
Delphinine, 652
Delphinium staphisagria, 652
Delphinoidine, 652
Delphisine, 652
Dementia, in ergotism, 511
Demerol, 358-361
Demulcents, 191-193
aluminum salts as, 122
preparations of, 193
Depilatory, thallium as, 150
Depressant, alcohol as, 254
Depressant, alcohol as, of central nervous system, 249
references to, 252
Depression, by drugs, 15
Dermatitis, following sulfonamide therapy, 735
Dermatology, use of drugs in, 802-807
Desiccated thyroid, action of, 542-545
preparations of, 548
therapeutic use of, 545-548
Desoxycorticosterone, 553, 554-555
use of, in Addison's disease, 556-557
Detergents, use of, as disinfectants, 777
Deuterium oxide, 46
Dextrose, 214
preparations of, 47
Dextrosum, 214
DFP, 458
Diabetes insipidus, 537
use of posterior-pituitary extract in, 539-540
Diabetes mellitus, 558
induction of, by alloxan, 563
treatment of, 560-561
use of salicylates in, 688
Diabetogenic hormone, of pituitary, 530
Diacetylamino-azotoluene, 800
Diacetylmorphine, 340
Diagnostic agents, 821
Dial, 318
Diaminobenzene, 726
Diamorphinæ hydrochloridum, 355
Diaphoresis, following use of salicylates, 691
Diaphoretic, use of ipecacuanha as, 720
use of opium as, 353
Diarrhea, and calcium absorption, 60
use of bismuth salts in, 157
use of hydrochloric acid in, 89
use of purgatives in, 238
Diarsenol, 180
Diasone, 731
Diastase, 222
Dibenzothiazine, 767
Dibucaine, 414
Dichloramine-T, 799
Dichlorodiphenyltrichloroethane, 814
Dichloroethylsulfide, 206
Dichlorophenarsine, 185
Dichlorophenol-indophenol, 603
Dick test, 821
Dicodide, 350
Dicumarol, 581-582
Diet, ketogenic, for urinary infections, 809
Diethylbarbituric acid, 316
Diethylmalonylurea, 316
Diethylstilbestrol, 566
Digestion, effect of alcohol on, 257
effect of lead salts on, 125
Digestive ferments, 220-224
Digilanid, 615, 640
Digitalinum verum, 615
Digitalis, 612-641
absorption of, 630-631
action of, 616-630
as antagonist to muscarine, 442

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Digitalis, assay of, 39, 40, 638
chemistry of, 613–616
comparison of, with quinidine, 709
contraindications to use of, 637
cumulative action of, 637
effect of, on heart, 618–623
excretion of, 630–631
history of, 612–613
LD_{50} of, 24
local effects of, 617
methods of administration of, 638–639
preparations of, 640–641
therapeutic use of, 631–637
tolerance to, 631
Digitalis folium, 640
lanata, 612, 615
pulverata, 640
purpurea, 612, 614
Digitalose, 614
Digitonin, 657
Digitoxigenin, 613, 614, 616
Digitoxin, 614
therapeutic use of, 639
Digitoxose, 614
Digoxigenin, 616
Dihydrocalciferol, 607
Dihydrocodeine, 350
Dihydrocodeinone, 350
Dihydroergosterol, 607
Dihydrohydroxycodeinone, 350
Dihydroisocodeine, 350
Dihydromorphinone, 349
Dihydroquinidine, 711
Dihydrotachysterol, 552, 608
Diiodo-hydroxyquinoline, 724
Diiodothyronine, 542
Diiodotyrosine, 542
Diisopropyl fluorophosphate, 458
Dilantin, 373–377
Dilaudid, 349
dose of, 351
therapeutic use of, 354
Dilling's formula, 25
Dimazon, 800
Dimercaprol, 176
Dimercaptopropanol, 176.
Dimethylaminoantipyrine, 673
Dimethylbenzyl ammonium chloride, 778
Dimethylethylcarbinol, 314
Dimethylsulfate, 206
Dinitrophenol, 660
Diodrast, 77
Dionea, 221
Dionin, 350
use of, in eye, 355
Diothane, 415
Diphenylchlorarsine, 206
Diphenylcyanarsine, 206
Diphenylhydantoin sodium, 373–377
therapeutic use of, 375–376
Diphtheria, use of digitalis in, 635
use of penicillin in, 749
Diphtheria antitoxin, 41, 819
Diphtheria toxin-antitoxin, 817
Diphtheria toxoid, 817
alum precipitated, 817
Diphyllobothriasis, 757
Diphyllobothrium latum, 757
Diodoquin, 724–725
Dioxyanthranol, 804
Dioxybenzoic acid, 692
Dioxybenzols, 805
Discs, 38
Diseptal A, 732
B, 732
C, 731
Disinfectants, 771–814
heavy metals as, 104
See also under specific drugs.
Disulon, 731
Diterpenes, 207
Dithranol, 804
Diuresis, following desiccated thyroid, 544
following posterior-pituitary extracts, 536
Diuretics, acetates as, 84
caffeine as, 398–399
citrates as, 84
digitalis as, 636
mercury as, 142
minor, 403
saline, 52–53
Diuretin, 400
Divinyl ether, 292–293
Dolantin, 358–361
Donovan's solution, 177, 178
Doryl, 449
Dose, by Dilling's formula, 25
effect of age on, 25
effect of sex on, 25
factors affecting, 25
by Young's formula, 25
Dover's powder, 352, 353, 721
Dracunculosis, 767
Drastics, preparations of, 246
Dropsy. *See* Edema.
Drosera, 221
action of camphor on, 210
effect of quinine on, 699
Drugs, absorption of, from mucous membranes, 31
action of, 13
general, 18
local, 18
remote, 18
administration of, by inontophoresis, 33
by intravenous route, 32
by inunction, 32
as pellets, 32
antagonism of, 28
biological assay of, 38
and biological variation, 23
chemical character of, 33
chemical constitution of, 20
concentration of, 17
conditions modifying the action of, 23
cumulative effect of, 27
definition of, 13
depressing, 15
disguising taste of, 30
distribution of, in body, 17
dose of, effect of size on, 24
effect of weight on, 24
effects of, after a meal, 25

Bharatiya Vidya Bhavan, New Delhi Collection

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Drugs, effects of, age and, 25
cumulative, 27
conditions modifying, 23
idiosyncrasy to, 26
menstruation and, 25
in pathological conditions, 28
sex and, 25
synergistic, 27
time of administration of, 26
tolerance to, 26
effect of lactation on, 25
elective affinity of, 18
general actions of, 18
hypodermic injection of, 32
idiosyncrasy to, 26
inhalation of, 31
irritation by, 15
LD_{50} of, 24
local action of, 29, 191
lungs and, 31
mechanism of action of, 19
method of action of, 15
methods of administration of, 29
optical isomerism in, 21
oral administration of, 30
pharmacological action of, 20
rate of absorption of, 30
rectal administration of, 31
remote actions of, 18
skin and, 29, 31
stimulating, 15
standard preparations of, 39
sublingual absorption of, 31
synergism of, 27
tolerance to, 26
use of, in pregnancy, 25
See also under specific items.
Dryobalanops aromatica, 210
Dryopteris filix-mas, 758
D-tubocurarine, 423
Duboisia, 464
hopwoodii, 429
myoporoides, 464
Dusting powders, bismuth salts as, 155
iodine-containing, 798
Dwarfism, 529
Dyes, acridine, as antiseptics, 801
triphenylmethane, 802
use of, as antiseptics, 800–802
Dysentery, bacillary, use of sulfonamides in, 739
tropical, 719
Dysmenorrhea, use of analgesics in, 686
use of estrogens in, 569
use of progesterone in, 571
use of testosterone in, 572
Dyspepsia, use of acids in, 89
Dyspnea, cardiac, use of nitrites in, 649

E

E. coli, 746, 752
Ear, effect of chenopodium on, 761
effect of quinine on, 701
Easton's syrup, 115, 389, 708
Eber's papyrus, 612
Ecbolic, ergonovine as, 515–516
posterior-pituitary extract as, 539
quinine as, 707
Eccoprotic, 228
Ecgonine, 405
Eclampsia, use of avertin in, 306
use of magnesium sulfate in, 66
use of veratum viride in, 656
Eczema, nickel, 149
use of chrysarobin in, 803
Edema, of larynx, 88
pulmonary, use of oxygen in, 94
use of calomel in, 140, 142
Effusions, use of salicylates in, 695
Egg, use of, for preparing vaccines, 817
Ehrlich, 22, 182, 914
"Ehrlich's 606," 180
Elderflower, 216
Electrocardiogram, effect of digitalis on, 626
Electrophoresis, 33, 448
Electuaries, 37
11-Dehydro-17-hydroxycorticosterone, 553
Elixir aromaticum, 217, 268
glycyrrhizæ, 217
Elixiria, 37
Elixirs, 37
Elm, slippery, 193
Eloeoptene, 207
Embrocations, 37
Emetic, ammonium carbonate as, 85
antimony salts as, 160–162
apomorphine as, 364
copper as, 117
emetine as, 718
ipecacuanha as, 720
mustard as, 203
zinc salts as, 119
Emetinæ et bismuthi iodidum, 721
hydrochloridum, 721
Emetine, 717–721
action of, 717
bismuth iodide, 721
preparations of, 721
therapeutic uses of, 720
Emodin, 233
Emollients, 193–197
castor oil as, 231
therapeutic use of, 194
as vehicles, 194
Emphysema, use of oxygen in, 94
Emplastra, 38
Emplastrum colophonii, 196
sinapis, 203
Emulsa, 36
Emulsin, 216, 663
Emulsio chloroformi, 294
Emulsions, 30, 36
Emulsum olei morrhuæ, 589
Encephalomalacia, 610
Encepholopathia, saturnine, 128
Endocarditis, bacterial, use of penicillin in, 747
use of digitalis in, 635
Endocrines, preparations of, 526–575
See also under specific items.

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Endurance, effect of alcohol on, 255
Enema, quassia infusion as, 219
  salt solution, 50
Enemata, 29, 38
  use of demulcents in, 192
Entameba histolytica, 719, 720
Enterobiasis, 757, 763
  use of gentian violet in, 767
Enterobius vermicularis, 757, 763
Enzymes, effect of formaldehyde on, 810
  effect of mercury on, 140
  effect of quinine on, 699
  effect of salicylates on, 689
  digestive, 220
  magnesium in, 65
  pancreatic, 221
  vegetable, 221
  See also under specific enzymes.
Ephedra, 497
Ephedrine, 497–499
  mechanism of action of, 498
  methyl derivative of, 506
  preparations of, 499
  therapeutic uses of, 499
    in alcoholic intoxication, 265
Epidermophytosis, 754
  use of copper salts in, 117
Epilepsy, drugs used in, 373–379
  from use of absinthe, 209
  use of bromides in, 371
    of diphenhydantoin in, 375
    of nitrites in, 648
    of phenobarbital in, 376
Epinene, 506
Epinephrine, 13, 485–497
  antagonism of quinine and, 700
  assay of, 39
  mechanism of action of, 493
  preparations of, 496
  reversal of action of, by ergotoxine, 514
  rôle of, in inducing ventricular fibrillation, 279
  therapeutic uses of, 494
  toxicology of, 493
  use of, with local anesthetics, 416
Epistaxis, from use of salicylates, 690
Epsom salts, 239, 246
Equilenin, 566
Equilin, 566
Equinine, 706
Erethism, mercurial, 138, 141
Ergine, 509
Ergobasine, 508
Ergochrysin, 507
Ergoclavine, 509
Ergocristine, 508
Ergocristinine, 508
Ergoflavin, 507
Ergometrina, 518
Ergometrine, 508, 518
Ergometrinine, 508
Ergomonamine, 509
Ergonovine, 508
  action of, 515–516
  use of, as ecbolic, 518
Ergosine, 508
Ergosinine, 508
Ergosterol, 606–607
Ergostetrine, 508
Ergot, alkaloids of, 507–519
    action of, 511–516
    assay of, 39, 516
    chemistry of, 507–509
  preparations of, 518
  therapeutic uses of, 516–517
  toxicology of, 509–510
Ergotamine, 507–508
  therapeutic use of, 517
Ergotaminine, 508
Ergothionine, 507
Ergotinine, 507–508
Ergotism, 509–510
Ergotocine, 508
Ergotoxine, 508, 511, 518
  ethanesulphonate, 518
Ergotrate, 518
Errhines, 29
Erysipelas, 738
  streptococcus antitoxin, 819
Erythrityl tetranitris, 650
Erythrol tetranitrate, 642, 648, 650
Erythromelalgia, in arsenic poisoning, 168
Erythrophlœum, 612
Erythroxylon coca, 404
Eseridine, 451
Eserine, 451
Esophagus, perforation of, 87
Espundia, 162
Esterase, inhibition of, by physostigmine, 455
Estivo-autumnal malaria, 704
Estradiol, 565–566
  benzoate, 566
Estradiolis benzoas, 569
Estriol, 565–566
  glycuronide, 566
Estrogens, 565–570
  chemistry of, 565
  physiology of, 567–568
  preparations of, 569–570
  synthetic, 566–567
  therapeutic use of, 568–569
Estrone, 565–566
  sulfate, 566
Estronum, 569
Ethanol. *See* Ethyl alcohol.
Ether, action of, 272
  as anesthetic, 269–310
    symptoms of, 270
  effect of, on blood, 279
    on blood vessels, 278
    on heart, 277
    on pupil, 280
    on respiration, 273
  excretion of, 283
  preparations of, 293
  references to, 294–295
  spirits of, 291
Ethinyl estradiol, 566
  testosterone, 570
Ethyl alcohol, 252–268
    absorption of, 258
    action of, 252–258
    as anesthetic, 266

Bharatiya Vidya Bhavan, New Delhi Collection

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Ethyl alcohol, blood content of, and degree of intoxication, 255
chronic use of, 263
effect of, on body temperature, 262
on growth, 260
on progeny, 260
on susceptibility to infections, 261
excretion of, 258
as food, 259
hepatotoxic effects of, 261
metabolism of, 260
preparations of, 268
references to, 268–269
therapeutic uses of, 265
tolerance to, 262
treatment of intoxication by, 265
use of, as disinfectant, 778
as vehicle, 266
aminobenzoate, 415
apocupreine, 701
bromide, 293
carbamate, 314
chaulmoograte, 651
chloride, 291
as local anesthetic, 202
dichlorarsine, 206
ether. *See* Ether.
hydrocupreine, 701, 704
iodoacetate, 206
mecurithiosalicylate, 788
morphine, 350, 355
nitrite, 648
oxide, 294
sulfathiazole, 731
Ethylene, as anesthetic, 300–303
dibromide, 293
tetrachloride, 766
Eucaine, 413–414
Eucalyptol, 207, 216
Eucalyptus, 227
oil of, 209
Eucatropine, 464, 482
Eucodal, 350
Eudoxine, 798
Eugenol, 218
Eumydrine, 464
action of, 477–478
Euphorbic acid, 206
Euphorbin, 206
Euphthalmine, 482
Euquinine, 707
Euresol, 805
Europhen, 798
Eurotium oryzæ, 222
Eusol, 799
Evipal, 318
Evipan, 318
Exanthemata, following use of quinine, 702
Excrement, disinfection of, 777, 810
Excretion, of ammonium salts, 57
of chloroform, 283
of ether, 283
of iodides, 72
See also under specific drug.
Exophthalmic goitre. *See* Graves' disease.
Expectorants, ammonium salts as, 58
Expectorants, apomorphine as, 364
balsam of Tolu as, 807
benzoic acid as, 697
benzoin as, 807
camphor as, 213
ipecacuanha as, 720
pilocarpine as, 462
potassium bicarbonate as, 82
squill as, 637
tar as, 806
Extracta, 37
liquida, 37
Extracts, 37
flavoring, 215
Extractum cinchonæ, 707
hepatis, 578
liquidum, 578
siccum, 578
malti, 214
cum oleo vitaminato, 589
pituitarii liquidum, 540
Extralin, 579
Extrasystoles, induced by digitalis, 627
Eye, in ariboflavinosis, 595
effect of chloroform on, 280
of cocaine on, 410
of digitalis on, 617
of dinitrophenol on, 660
of epinephrine on, 491
of ether on, 280
of methyl alcohol on, 267
of naphthol on, 804
of quinine on, 701
of salicylates on, 690
mercury ointments for use in, 144
spectacled, in rat, 600
See also under specific drugs.

F

Fainting, use of acetic acid in, 91
Familial periodic paralysis, 55
Feathers, effect of desiccated thyroid on 545
Feces, lead content of, 126
Fel bovis, 224
Female sex hormones, 564–571
Fennel, 216
Ferments. *See* Enzymes.
Fern, male, 758
Ferri et ammonii citrates, 114
Ferrocyanides, 664
Ferrous carbonate, 113
gluconate, 113
lactate, 113
salts, 113
sulfate, 113
Ferruginous pills, 114
Ferrum reductum, 114
Ferula sumbul, 213
Fever, effect of digitalis on, 630
following use of quinine, 702
use of alcohol in, 266
of antipyretics in, 684–685
of digitalis in, 635
Fibrin, 582

Bharatiya Vidya Bhavan, New Delhi Collection

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Fibrin, foam, 582
human blood, 820
Fibrinogen, 582
plastics, 820
Ficin, 757, 763, 767
Fig, 221
bastard, 767
Filariasis, 163
Filicic acid, 758
Filix-mas, 758, 768
Filmaron, 758
Filtrate factor, 598
Fiscus laurifolia, 767
Fish-oil, as source of vitamin D, 607
Flavaspidic acid, 758
Flavaspidin, 758
Flavones, 604
Flavoring substances, 215
Flavoxanthin, 585
Fluidextracta, 37
Fluidextracts, 37
Flukes, 758
Fluorides, 68
Flutter, auricular, use of digitalis in, 633
Flying blister, 204
Fœniculi, 216
Folic acid, 601-602
use of, in agranulocytosis, 677
Follicle stimulating hormones, of pituitary, 529
Food, alcohol as, 259
iron in, 109
Formaldehyde, as disinfectant, 810
as urinary antiseptic, 808
Formalin, 810
Formic acid, 91
"Fourneau 309," 185
"Fourneau 933," 515
Fowler's solution, 175, 177
Foxglove. *See* Digitalis.
Frambesia, 182
Frangula, 233
Frei test, 822
Friar's balsam, 807
Friedländer's bacillus, 746
Friedländer's infection, use of sulfonamides in, 737
Frog, effect of salicylic acid on, 689
Fructose, 214
Fuadin, 162-163
Fuller's earth, 194
Fumigatin, 755
Fungicide, copper as, 117
Fungus diseases, 74

G

Galactogogue, posterior-pituitary liquid as, 537-538
Gallic acid, 224
Gallol, 122
Gambir, 227
Gangrene, from use of ergot, 510
Ganja, 361
Gargarismata, 29
Gargle, 29
Gargle, aluminum salts as, 122
demulcents as, 192
Gas gangrene antitoxin, 41, 819
Gases, war, 206
Gastric ulcer, 81
Gastritis, 81
Gastro-intestinal tract, action of arsenic on, 169
of colchicum on, 667
of ergot alkaloids on, 512
See also under specific drugs.
Gaultheria procumbens, 687
Gelatin, 820
use of, as demulcent, 192
Gelose, 244
Gelsemicine, 428
Gelseminine, 428
Gelsemium, 428
Geneserine, 451
Genins, 613
Genito-urinary tract, antiseptics for, 807-810
use of antiseptics in, 776
Genoscopolamine, 477
Gentian, 219
Gentian violet, 757, 802
preparations of, 768
use of, as anthelmintic, 767
Gentiana, 219
lutea, 219
Germanin, 185
Germanium, 151
Gigantism, 528
Gin, 262
Ginger, 216, 217
paralysis, 784
Gitalin, 614
Gitonin, 657
Gitoxigenin, 614, 616
hydrate, 614
Gitoxin, 614
Glands, effect of histamine on, 524
secretory, action of atropine on, 467
Glauber's salt, 239, 246
Glaucoma, induction of, by atropine, 470
use of carbaminoylcholine in, 450
use of DFP in, 458
Gliotoxin, 755
Globin insulin, 561
Globucid, 731
Globulin, human blood, 820
Glossitis, 594
Glucokinin, 559
Glucose, formula of, 614
use of, in adrenal insufficiency, 553, 556
in hypoglycemia, 560
Glucosides, 34
Glutamic acid hydrochloride, 89
Glycerina, 37
Glycerine, 196, 231
toxicity of, 233
Glycerinum, 196
acidi borici, 794
boracis, 794
phenolis, 782
Glycerita, 37
Glycerites, 196

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Glyceritum amyli, 193
boroglycerini, 794
Glycerophosphates, 244
Glyceryl trinitrate, 647
Glycine, 696
Glycocol-phenetidine, 674
Glycosides, 34
Glycuronic acid, 696
Glycyrrhiza, 193
Glycyrrhizin, 193
Gnoscopine, 329
Goa powder, 803
Goitre. *See* Thyroid.
Goitrogenic drugs, 549
Gold, salts of, 147
sodium thiosulfate, 147
Golden seal, 657
Gonadotrophins, 563–564
of pituitary, 529
Gonorrhea, 737, 740
treatment of vaginitis in, 569
use of penicillin in, 748
of permanganate in, 792
of silver salts in, 789
Gout, in lead poisoning, 129
use of alkalies in, 82
of colchicum in, 669
of neocinchophen in, 672
Gramicidin, 753
S, 753
Gram-negative bacteria, action of sulfamylon on, 731
Granuloma inguinale, 162
use of podophyllum in, 237
Graves' disease, 73
use of iodine in, 74
use of radoactive iodine in, 75
Gray powder, 146
Green hellebore, 654
Gregory's powder, 244
Growth, effect of arsenic on, 173
Growth hormone, of pituitary, 528–529
Guaiacols, 805
Guanidine, 457
Guarana paste, 394
Guinea worm, 767
Gulonic acid, 602
Gum acacia, 820
Gumma, 74
Gum-resins, 34
Gums, hyperplasia of, following use of diphenylhydantoin, 377
Gun-cotton, 196
Gynergen, 517
Gypsophila struthium, 656

H

Habit, from sedatives and hypnotics, 314–315
Hæmatoxylon, 227
Hæmophilus influenzæ, 744
Haffnium, 152
Hair, greying of, 599
pigmentation of, 600
Halazone, 813
Halibut-liver oil, 586, 589
Hamamelis, 227
Hard soap, 196
Harrington's solution, 786
Hashish, 361, 393
Hay-fever, use of propadrine in, 505
Headache, use of acetylsalicylic acid in, 693, 695
of antipyretics in, 677
of nitrites in, 649
Hearing, effect of quinine on, 701
effect of salicylates on, 689–690
Heart, effect of aconitine on, 653
of alcohol on, 257
of anesthetics on, 276
of atropine on, 472
of camphor on, 211
of cyclopropane on, 304
of digitalis on, 618–623
of hypnotics on, 311–312
of pamaquine on, 715
of quinine on, 700
of quinidine on, 709
of salicylates on, 690
of sedatives on, 311–312
hypertrophy of, effect of digitalis on, 636
regulatory nerves of, 431
See also under specific drugs.
Heart-block, induced by digitalis, 627–629
use of digitalis in, 637
Heart disease, use of calomel in, 140
use of oxygen in, 94
Heart failure, effect of digitalis in, 626
use of ammonia in, 86
Heat, cramps, 50
as disinfectant, 813
Heavy water, 46
Helium, 100
Helleborus niger, 612, 654
Hematics, 573–582
Hematoporphyrin, 126, 662
Hematoporphyrinuria, following use of sulfonal, 314
Hematuria, following use of mandelic acid, 809
Hemoglobinuria, following use of quinine, 702
Hemolysis, from arsine, 174
Hemophilus influenzæ, 738
Hemorrhage, following use of salicylates, 689
in phosphorus poisoning, 188
Hemostatics, 582
use of ferric chloride as, 113
use of kephrine as, 504
Hemp, 361
Henbane, 463
Hepaflavin, 594
Hepar sulphuris, 70
Heparin, 580
Hepatitis, from use of cinchophen, 671
use of choline in, 445, 601
Heredity, use of alcohol and, 260
Heroin, 340
Herpes, in arsenic poisoning, 168
Herxheimer reaction, 178

Bharatiya Vidya Bhavan, New Delhi Collection

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Hesperidin, 217, 604
Heterogenous syndrome, 21
Hexahydrocyclohexane, 601
Hexamethylenetetramine, 808
Hexamina, 808
Hexamine, 808
Hexavitamin preparations, 584
Hexestrol, 566
Hexobarbitonum, 327
Hexylresorcinol, 757, 766
  preparations of, 768
Hippulin, 566
Hippuran, 77
Hippuric acid, 696
  test, 697
Hirudin, 580
Histaminase, 524
Histamine, 519–525
  administration of, by iontophoresis, 448
  drug antagonism to, 521
  therapeutic uses of, 525
  toxicity of, 521
Histone insulin, 561
Hock, 268
Hodgkin's disease, 206
Hoffmann's drops, 291
Holocaine, 414
Homatropine, action of, 477
  chemistry of, 464
Homatropinemethylbromide, 478
Homosulfanilamide, 731
Honey, 214
Hookworm, 757
  use of carbon tetrachloride in, 764–766
  use of hexylresorcinol in, 766
  use of thymol in, 760
Hops, 268
Hordeum, 193
Horehound, 216
Hormones, 526–575
  chemistry of, 526
  male, 571–573
  method of administration of, 527
  See also under specific items.
Hyclorite, 800
Hycodan, 350
Hydnocarpic acid, 650–651
Hydnocarpus anthelmintica, 650
  wightiani, 650, 652
Hydragogue, 228
Hydrargyri bichloridum, 145, 786
  chloridum, 145
  mite, 145
  oxidum flavum, 145
  perchloridum, 787
  salicylas, 145
  succinimidum, 145
Hydrargyrum, 145
Hydrastine, 657–658
Hydrastinine, 657–658
Hydrastis, 657
  canadensis, 657
Hydrates, of alkalies, 78–83
Hydrochloric acid, 87, 90
    use of, in achlorhydria, 89–90
Hydrocholeretics, 222
Hydrocotarine, 329
Hydrocyanic acid, 663–650
    action of, 664
    effect of, on metabolism, 665
    poisoning by, treatment of, 665–666
      use of copper as antidote in, 118
Hydrogen dioxide, 790–791
  peroxide, 790–791
  phosphide, 189
  sulfide, 69
Hydrogenii peroxidi, 791
Hydrolysates, of protein, 821
Hydrophobia, 816
Hydroquinone, 692, 781, 805
Hydrosulphuric acid, 69
Hydrous wool-fat, 195
Hydroxethylapocupreine, 701
Hydroxyquinoline derivatives, use of, in amebiasis, 723–725
Hydroxytoluic acid, 809
Hymenolepis nana, 757
Hyoscine, 463
  action of, 476–477
  preparations of, 484
  therapeutic uses of, 481–482
Hyoscyamine, 463
  action of, 475–476
Hyoscyamus niger, 463
Hyoscyamus, preparations of, 483–484
Hypercalcemia, 550
Hyperchlorhydria, 80
Hyperparathyroidism, 551
Hypertension, induced by lead, 128
  use of nitrites in, 648
Hyperthermia, induction of, 661
Hypertonic solution, 48
Hypervitaminosis, 607
Hypnal, 673
Hypnotic, 310–327
  avertin as, 306
  preparations of, 327–328
  references to, 328
  therapeutic use of, 324–325
  tolerance to, 314
Hypochlorites, 813
Hypochlorous acid, 799
Hypodermic method, 32
Hypoglycemia, symptoms of, 560
Hypoparathyroidism, 551
Hypophosphites, 244
Hypophysis. *See* Pituitary.
Hypoquebrachine, 659
Hypothalamus, as regulator of body temperature, 680
Hypothrombinemia, following use of salicylates, 689
Hypothyroidism, 541, 546
Hypotonic solution, 48

I

Iceland moss, 193
Ichthammol, 806
Ichthyol, 806
Icterus, following use of male fern, 759
Idiosyncrasy, to acetylsalcylic acid, 693
  to aminopyrine, 677

Bharatiya Vidya Bhavan, New Delhi Collection

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Idiosyncrasy to drugs, 26
to quinine, 702
Ileus, use of posterior-pituitary extract in, 539
Ilex paraguayensis, 394
Imidazole, derivative of, 507
Immunity, active, 816
passive, 818
Immunization, 816
Impotence, use of yohimbine in, 659
Indian squill, 641
Infection, in avitaminosis, 604
effect of alcohol, on susceptibility to, 264
Infiltration anæsthesia, 419
Inflammation, chronic, 75
local, treatment of, 202
therapeutically induced, 201
Influenza, use of analgesics in, 686
vaccines for, 817
Infusa, 36
Infusions, 36
Infusum concentratum, 36
digitalis recens, 640
recens, 36
Injectio diethylstilbestrolis, 569
hepatis, 578
insulin, 562
insulini protaminati cum zinco, 562
parathyroidei, 552
quininæ et urethani, 708
Inorganic substances, action of, 43
Inositol, 600
Insecticides, 68, 814
Insulin, 558–562
action of, 559–560
administration of, 561
assay of, 39, 40, 562
chemistry of, 558–559
crystalline zinc, 561
dosage of, 562
globin, 561
preparations of, 562
protamine, 561
regular, 561
therapeutic uses of, 560–561
Insulinum, 562
Intermedin, 535
Internal secretions. *See* Hormones.
International unit, for carotene, 588
for gonadotropins, 564
for penicillin, 745
for vitamin A, 588
for vitamin B, 593
for vitamin D, 608
Interrenalin, 554
Intestinal antiseptics, sulfonamides as, 729-730
Intestine, action of alkalies on, 79
action of volatile oils on, 208
in arsenic poisoning, 169
effect of anesthetics on, 281
of atropine on, 471
of bismuth salts on, 155
of heavy metals on, 105
of mercury on, 139
in phosphorus poisoning, 189
Intestine, post-operative atony of, drugs in, 238
use of antiseptics in, 775
Intocostrin, 426-427
use of, in anesthesia, 309
Intoxication, by alcohol, 263
blood concentration in, 255
treatment of, 265
by digitalis, 638
Intravenous injection, 32
Inunction, 32
with mercury, 142
Iocamfen, 798
Iodates, as oxidizing disinfectants, 795
Iodides, 70–76
use of, in goitre, 74
in malingering, 75
in syphilis, 74
Iodine, 70–76
aqueous solution of, 78
local use of, 75
organic derivatives of, 76
radioactive, 75
tincture of, 78
use of, as antiseptic, 796
for diagnostic purposes, 77
in radiography, 76
weak solution of, 78
Iodism, 70
Iodoacetone, 206
Iodobehenate, 76
Iodobenzoic acid, 697
Iodobismitol, 158
Iodo-casein, 542
Iodo-chlor-hydroxyquinoline, 724
Iodoform, 797–798
Iodoformum, 798
Iodo-hydroxyquinoline sulfonic acid, 723
Iodol, 798
Iodophthalein, 236
Iodothyroglobulin, 542
Iodoxylum, 77
Iodum, 77
Iontophoresis, 448
Ipecac, 717–721
Ipecacuanha, 717–721
pulverata, 721
use of, in alcoholism, 265
Ipomœa, 246
orizabenzis, 246
purga, 246
Ipral, 318
Irgamid, 731
Iris, innervation of, 468
Irish moss, 193
Iron, 107–115
absorption of, 109
action of, 108
administration of, 112
amount of, in body, 108
dosage of, 113
excretion of, 109
fate of, in body, 110
pharmacology of, 107
preparations of, 112, 114–115
radioactive, 111
reduced, 113

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Iron, therapeutic use of, 111
Irritants, local, alcohol as, 252
therapeutic use of, 201
Irritation, by drugs, 15
Isinglass plaster, 196
Iso-alloxazine, 594
Isonipecaine, 358–361
Isonitriles, 664
Isophysostigmine, 451
Isopilocarpine, 459
Isopropyl alcohol, as disinfectant, 778
apocupreine, 701
Isopunicine, 759
Isotonic solutions, therapeutic use of, 50
Isotopes, use of radioactive, 152
Itching, pilocarpine for relief of, 462
Ivy, poison, 205

J

JALAP, 236–237
Jalapa, 246
Jalapin, 236
Japaconitine, 652
Jasmine, 428
Jateorrhiza palmata, 219
Jaundice, hemorrhagic tendency in, 610–611
Jaw, necrosis of, in mercury poisoning, 139
in phosphorus poisoning, 188
Jequirity, 823
Jervine, 654, 656
Jesuit's drops, 807
Jimson weed, 463
Juniper, 216
oleum, 216
Juniperi, 216

K

KAIRINE, 673
Kairoline, 673
Kala azar, 162
Kali nuts, 451
Kamala, 758
Kaolin, 194, 227
poultice of, 197
Kava kava, 220
Kephrine, 504
Keratitis, 595
Keratomalacia, 587
Keratosis, follicular, 587, 588
Kesotoxin, 758
Ketohydroxyestrin, 569
Ketosis, following use of salicylates, 690
Kidney, cortical necrosis of, 736
effect of alcohol on, 262
of anesthetics on, 281
of chloroform on, 281
of choline deficiency on, 601
of colchicine, 668
of digitalis on, 624
of ether on, 281
of heavy metals on, 105
of lead on, 128
of mercury on, 140
Kidney, effect of nitriles on, 645
of sulfonamides on, 735
excretion of alcohol by, 259
in phosphorus poisoning, 189
Kidney stones, 82
Kieselguhr, 194, 197
Kino, 226
Koagulation vitamin, 610
Kola nut, 394
Kombé strophanthus, 612
Kousso, 758
Krameria, 226
Kryofine, 674
Krysolgan, 147
K-strophanthin, 615

L

L. CASEI factor, 601
Labarraque's solution, 800
Labiatæ, 207
Laburnum, 429
Lacquer tree, 205
Lacrimators, 206
Lactates, 83
Lactation, use of drugs in, 25
Lactic acid, 91
Lactobacillus casei, 602
Lactoflavin, 593
Lactogenic hormone, of pituitary, 529
Lactophenine, 674, 676
Lactose, 214
Lactosum, 214
Lactyl phenetidine, 674
Lævulosum, 214
Lamellæ, 38
atropinæ, 484
physostigminæ, 458
Lanatoside, 615
C, therapeutic use of, 640
Lanolin, 195
Lanthanum, 152
Lanthopine, 329
Lappaconitine, 653
Larch tree, 479
Lard, 194
benzoinated, 195
Larocaine, 413–414
Laudanine, 329
Laudanosine, 329, 658
Laudanum, 355, 356
Laughing gas, 295
Lavender, 216
Laxatives, 228
See also under specific items.
"LD_{50}," 24
Lead, 123–131
acetate, 131
colic, 126
poisoning by, 123–131
treatment of, 130
sugar of, 131
tetraethyl, 129
therapeutic use of, 129
triethyl, 129
Leche de higueron, 757, 763, 767–768

Bharatiya Vidya Bhavan, New Delhi Collection

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Lecithin, 444, 601
action of saponins on, 656
Leishmaniasis, use of tartar emetic in, 162
Lemon, 216
juice, 92
Lentin, 449
Leprosy, use of chaulmoogra oil in, 650–651
use of promin in, 651, 731
Leptazol, 392
Lethal dose, of drugs, 24
Leukemia, in benzol poisoning, 663
chronic myelocytic, use of arsenic in, 175
Leukocytes, effect of quinine on, 699, 702
Leukopenia, following sulfonamide therapy, 735
use of folic acid in, 602
Levulose, 214
Lichen planus, use of chrysarobin in, 803
Lily of the valley, 612
Lime, chlorinated, 813
deficiency of, 60
salts of, 59
unslaked, 813
water, 62, 63
Limes, juice of, 92
Liniment, 37
ammonia, 85
camphor, 212, 213
turpentine oil, 202
Linimenta, 37
Linimentum aconiti, 654
camphoræ, 241
et saponis, 196
chloroformi, 294
saponis, 196
mollis, 196
terebinthinæ, 203
Linseed, 193
Linum, 193
Lipiodol, 76
radiologique, 77
Lipotropic action, of choline, 444
of inositol, 601
Liquid, paraffin, 245
petroleum, 245
Liquidambar orientalis, 807
Liquor ammoniæ, 86
calciferolis, 608
cresolis saponatus, 784
folliculi, 565
formaldehydi, 811
hepatis, 578
hydrogenii peroxidi, 791
fortior, 791
iodi fortis, 797
mitis, 797
simplex, 797
quininæ ammoniatus, 708
sodæ chlorinatæ chirurgicalis, 800
sodii hypochloritis, 800
vitaminorum A et D, 589
Liquores, 36
Liquorice, root, 193
use of, as demulcent, 193
Lithium, salts of, 55
Lithium, stibiothiomalate, 163
Liver, amebic abscess of, 721
cirrhosis of, 601
effect of alcohol on, 265
of arsenic on, 172
of chloroform on, 283
of choline deficiency on, 601
of cincophen on, 671
of ether on, 283
of mercury on, 140
extracts of, in agranulocytosis, 677
in phosphorus poisoning, 188–189
preparations of, 575–578
assay of, 40, 576
dose of, 576
therapeutic use of, 577
of sulphur, 70
use of, in anemia, 573–575
Lobelia inflata, 429
therapeutic use of, 437
Lobeline, 429
Local action, of drugs, 18, 29
Local anesthetics, 404–423
antipyrine as, 678
quinine as, 707
therapeutic use of, 416–421
See also under specific drugs.
Loeffler's syndrome, use of emetine in, 722
Logwood, 227
Loretin, 724, 798
Losophan, 798
Lotions, 37
Lozenges, 38
Lugol's solution, 74
dose of, 75
Luminol, 320–327
Lumisterol, 606
Lunasol, 789
Lungs, drugs and, 31
use of antiseptics in, 776
Lupus erythematosus, use of gold in, 147
Luteinizing hormone, of pituitary, 529
Lycaconitine, 653
Lymphogranuloma venereum, 738
Lymphoma, 206
Lysergic acid, 508–509
Lysol, 783
Lysozome, 755
Lytta vesicatoria, 204

M

Ma huang, 497
Mace oil, 216
Magisterium bismuthi, 159
Magma, 36
magnesiæ, 246
Magnesia, milk of, 83
Magnesii carbonas, 246
liquor citratis, 246
oxidum, 83, 246
phosphas tribasicus, 83
sulfas, 246
Magnesium, antagonism to calcium, 61
carbonate, as antacid, 81
as cathartic, 239, 242

Bharatiya Vidya Bhavan, New Delhi Collection

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Magnesium, oxide, as antacid, 81
as cathartic, 239, 242
phosphate, as antacid, 81
preparations of, 83
salts of, 65–66
sulfate, as cathartic, 239
therapeutic use of, 66
trisilicate, as antacid, 81
Malakine, 674
Malaria, 704–705
therapy of, 705–707, 711–717
Male fern, 757, 758–759
sex hormones, 571–573
Malingering, use of iodine to detect, 75
Mallotus philippinensis, 758
Malnutrition, use of protein hydrolysates in, 821
Malodorous volatile oils, 213
Malonates, 68
Malt, extract of, 214
Maltzyme, 222
Mammary glands, effect of sex hormones on, 568
Mandelic acid, 809
Manganese, 148–149
poisoning by, 149
Manicheel tree, 206
Manna, 507
Mannite, 507
Mannitol hexanitrate, 642, 648, 650
Mapharsen, 183–184
Marble bone, 551
Marfanil, 731
Marihuana, 361
Marshmallow, 193
Masked iron, 107
Massæ, 37
Masses, 37
Materia medica, 15
May apple, 246
Measles, vaccines for, 817
Mecholine, 447–449
Mecholyl, 447–449
Meconidine, 329
Medicated vinegars, 37
waters, 36
Mel, 214
boracis, 794
depuratum, 214
Melanphores, effect of posterior-pituitary liquid on, 535–536
Melanosis, arsenic, 168, 172
Melarsen, 186
Mellita, 36
Menadione, 611
Menadioni sodii bisulfas, 612
Menaphthone, 612
Menaphthonum, 612
Ménière's disease, 548
use of potassium salts in, 55
Meningitis, use of penicillin in, 747
use of sulfathiazole in, 728
Meningococcic infection, use of penicillin in, 747
use of sulfonamides in, 737, 738, 740
Menispermine, 218
Menopause, use of estrogens in, 568
Menopause, use of testosterone in, 572
Menorrhagia, use of progesterone in, 571
Menstruation, effect of estrogen on, 569
Mentha viridis, 216
Menthol, 210, 213
Mepacrinæ hydrochloridum, 714
methanosulphonas, 714
Mepacrine, 711–714
hydrochloride, 714
Meralluride sodium, 143
Merbaphen, 143
Merbromin, 787
Mercuhydrin, 143
Mercupurin, 143
Mercurialism, 136
Mercurials, organic, 787–788
Mercuric chloride, 774
use of, as antiseptic, 785–786
cyanide, 786
oxide, 786
periodide, 786
Mercurin, 142–143
Mercurochrome, 787
Mercurophylline, 142–143
Mercurous chloride, 140, 142, 145
Mercury, 135–147
action of, on nervous system, 141
acute corrosive poisoning, 135
and chalk, 145, 146
compounds of, as antiseptics, 785
as diuretics, 142–143
organic, 787–788
contraindications to use of, 144
distribution of, in body, 141
elimination of, 141
poisoning by, 135–138
treatment of, 144
preparations of, 145–147
as purgative, 139–140, 142
salicylate, 145
therapeutic uses of, 142
Merphenyl borate, 787
nitrate, 787
picrate, 787
Mersalyl, 143
Mersalylum, 146
Merthiolate, 788
Mescal buttons, 362
Mescaline, 362
Mestibol, 566
Mesudin, 731
Metabolism, action of arsenic on, 172
of alcohol, 258
in anesthesia, 282
effect of antipyretics on, 679
of cyanide on, 665
of desiccated thyroid on, 544
of epinephrine on, 492
of quinine on, 703
of salicylates on, 692
of strychnine on, 386
poisons increasing, 660
Metadinitrobenzol, 662
Metadioxybenzol, 805
Metalloids, 154–190
Metals, heavy, 100–107
absorption of, 104

Bharatiya Vidya Bhavan, New Delhi Collection

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Metals, heavy, action of, 105
excretion of, 104
local action of, 101
therapeutic use of, 106
minor, 147–154
Metamorphosis, acceleration of, by thyroid, 545
Metamucil, 244
Meta-oxybenzoic acid, 693
Metaphen, 788
Methane, narcotics, 249
Methemoglobin, 662, 676
Methemoglobinemia, following use of pamaquine, 715
Methenamina, 808
Methenamine, 808
Methiodal, 77
Methionine, 601, 821
Methyl alcohol, 267–268
arbutin, 403
bromide, 100
coniine, 428
dihydromorphinone, 350
ephedrine, 506
glycolic phenetidine, 674
guanidine, 457
hordenine, 429
morphine, 350
oxymethyl salicylate, 692
rosanilinæ chloridum, 768
rosaniline, 767
salicylate, 687, 688, 692, 695
selenide, 151
sulfathiazole, 731
sulphonal, 315
telluride, 151
testosterone, 572, 573
violet, 767, 802
Methylated spirit, 268
Methylene blue, use of, in cyanide poisoning, 666
Methylis salicylas, 695
Metopon, 350
Metrazol, 392
Metrorrhagia, use of progesterone in, 571
Metycaine, 413, 415
Mexican scammony, 246
Meyer-Overton, theory of narcosis, 249–250
Mezereum, 205
Micro-aerophilic infections, use of zinc peroxide in, 791
Migraine, use of caffeine in, 400
use of ergotamine in, 517
Milk, irradiated, 607
of magnesia, 83
as source of vitamin B, 590
stimulation of secretion of, by posterior-pituitary liquid, 537
Milks, 36
Mineral waters, 244
Miotic, pilocarpine as, 461
Mistura magnesii hydroxidi, 83
Misturæ, 36
Mithridatism, 26
Mixtures, 36
Molybdenum, 150
Monilia albicans, 754
Monkey, effect of estrogens in, 567
Monkshood, 652
Monomestrol, 566
Morphinæ sulfas, 355
Morphine, absorption and excretion of, 341-343
abstinence syndrome, 347
action of, 331-334
addiction to, 344-345
treatment of, 348
chemistry of, 329-330
chronic poisoning by, 345
dose of, 351
effect of, on alimentary canal, 338–340
on metabolism, 341
on smooth muscle, 340–341
habit, 345-348
poisoning by, 343
treatment of, 343-344
symptoms from, 330-331
tolerance to, 344-345
use of, in anesthesia, 309
in lead colic, 130
Moss, Iceland, 193
Irish, 193
Mucilagines, 36
Mucilago acaciæ, 193
tragacanthæ, 193
Mucous membranes, action of alcohol on, 253
Mucuna urens, 451
Multiple myeloma, 206
Muscarine, 440–444
toxicology of, 443
Muscarine action, 441
Muscle, action of caffeine on, 396
dystrophy of, in vitamin E deficiency, 609
effect of alcohol on, 257
of ammonium salts on, 57
of quinine on, 700
of veratrine on, 655
Mushrooms, poisonous, 440, 444
Mustard, 203
black, 203
gas, 206
nitrogen, 206
Mutation, induced by colchicine, 669
Myasthenia gravis, 55
effect of quinine in, 700
use of neostigmine in, 456
Mydriatic, use of paredrine as, 505
Myocarditis, use of digitalis in, 635
Myochrysine, 147
Myoctonine, 653
Myristica, 216
Myristicæ, 216
Myristicin, 207
Myrosin, 203
Myroxylon pereiræ, 807
Myxedema, 541, 546
treatment of, 547

N

NAFTALAN, 806
Nagai-camphor, 210

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Nanthotoxin, 389
Naphthalene, 804
Naphthazoline, 507
Naphthols, as antiseptics, 804–805
Naphthoquinone, 611
Narceine, 329
Narcolepsy, use of amphetamine in, 501
Narcosis, theories concerning mechanism of, 250–252
Narcotics, of methane series, 249
  opium group of, 309
  See also under specific drugs.
Narcotine, 330, 658
National Formulary, 35
Necator americanus, 757
Necatoriasis, 757
Nematodes, 758
Neoarsphenamina, 186
Neoarsphenamine, 182
  toxicity tests of, 40
Neocinchophen, 670–672
Neocinchophenum, 672
Neodiarsenol, 182
Neodymium, 152
Neo-iopax, 77
Neonal, 319
Neoprontosil, 726
Neosalvarsan, 182
Neosilvol, 789
Neostal, 319
Neostam, 164
Neostibosan, 164
Neostigmine, 456–457
  as antidote to curare, 426, 427
Neosynephrin, 503
Nephritis, 738
  in chromium poisoning, 148
  lead, 128
  magnesium sulfate in, 66
  in manganese poisoning, 149
  from uranium, 150
  use of sulfanilamide in, 736
Nephrosis, use of protein hydrolysates in, 821
Nerium, 612
Nervous system, action of alcohol on, 253
    action of mercury on, 141
    action of volatile oils on, 209
Neuralgia, use of acetylsalicylic acid in, 693, 695
  use of aconitine in, 654
  use of antipyretics in, 677
Neuritis, peripheral, in arsenic poisoning, 168
    from lead, 127
    following sulfonamide therapy, 735
    following use of male fern, 759
New and Non-official Remedies, 35
Niacin, 595–597
Niacinamide, 595–597
Nickel, 149
  carbonyl, 149
Nicotiana tabacum, 429
Nicotin amide, 595–597
Nicotinamidum, 597
Nicotine, 429–437
  actions of, 430–438
Nicotine, as antagonist to curare, 424, 426
  poisoning by, 430
Nicotinic acid, 595–597
Night-blindness, 587
Nightshade, black, 657
Nikethamide, 392–393
Nirvanol, 374
  therapeutic use of, 377
Niter, spirits of, 648
  sweet spirit of, 650
Nitrates, 642
  as diuretics, 52
  toxicity of, 52
Nitre, 649
Nitric acid, 87, 90
Nitriles, 664
Nitrites, 642–650
  action of, on circulation, 643
    on kidneys, 645
    on respiration, 645
  excretion of, 646
  preparations of, 649–650
  of sodium, 647
  symptoms of, 642–643
  therapeutic use of, 648
  tolerance to, 647
Nitrobenzol, 661
Nitroethane, 642
Nitrogen, effect of alcohol on elimination of, 260
  mustards, 206
Nitrogenii monoxidum, 300
Nitroglycerin, 642–650
  action of, 647–649
Nitromethane, 642
Nitrous esters, 642
  oxide, 295–300
    action of, 296
    as anesthetic, 299
Norhyoscyamine, 464
Nornicotine, 429
Nortropine, 464
Nose, perforation of septum of, by arsenic, 169
Nosophen, 798
Nostal, 319, 328
Notatin, 754
Novarsenobenzol, 182
Novasurol, 143
Novatophan. *See* Neocincophen.
Novatropine, 478
  chemistry of, 464
Novocaine, 412
Nupercaine, 413–415
Nut-gall, 227
Nutmeg, 216
  oil of, 209
Nutrition, effect of arsenic on, 173
Nux vomica, preparations of, 387
Nyctalopia, 587, 588

O

Oak, poison, 205
Obesity, use of desiccated thyroid in, 547

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Obesity, use of dinitrophenol in, 660
Obstipation, use of desiccated thyroid for, 548
Oculenta, 38
Oculentum cocainæ, 422
iodoformi, 798
Œnanthe crocata, 389
Œnanthotoxin, 389
Œstradiolis monobenzoas, 570
Œstrone, 569
Œstronum, 569
Oidium asteroides, 754
Oil, of asafetida, 213
of birch, 216
castor, 231
of chenopodium, 757, 760
of copaiba, 808
cubebs, 808
ethereal, 207–209
fusel, 268
iodized, 77
of mustard, 203
of peppermint, 210
of sandalwood, 808
of thyme, 760
of turpentine, 202
of valerian, 213
of wintergreen, 216, 687, 688, 692
of wormseed, 760
of wormwood, 210
volatile, 216
as carminatives, 215–218
as flavoring agents, 215–218
malodorous, 213
series, 207–209
Ointments, 29, 38
citrine, 144
emollient, 194
mercury, 144
simple, 195
white, 120, 195
Old tuberculin, 41
Oleander, 612
Oleatum hydrargyri, 145
Oleoresin, 34
of aspidium, 757, 758–759
Oleoresina aspidii, 768
Oleovitamina A, 589
A et D, 589
D Synthetica, 608
Oleum amygdalæ amaræ, 216
expressum, 195
aurantii, 216
chaulmoogræ, 651
chenopodii, 768
gossypii seminis, 195
hippoglossi, 589
hydnocarpi, 652
iodatum, 76, 78
iodisatum, 78
lavandulæ, 216
limonis, 216
morrhuæ, 589
non-desterarinatum, 589
olivæ, 195
picis rectificatum, 806
ricini, 244
Oleum rosæ, 216
rosmarini, 216
terebinthinæ rectifactum, 203
theobromatis, 196
vitaminatum, 589
Oligodynamic action, 104
Oliguria, from barbiturates, 321
Olive oil, 195
Omnopon, 351
Onchocerciasis, 164
Ophthalmia, use of silver salts in, 134, 788
neonatorum, 134
Opianic acid, 658
Opisthotonus, in strychnine poisoning, 380
Opium, 329–357
addiction to, 344–345
camphorated tincture of, 217
chronic poisoning by, 345
composition of, 329
compound mixture of, 162
compounds of, 350–351
derivatives of, 329–355
preparations of, 355–356
references to, 356–358
therapeutic use of, 351–355
dry extract of, 356
granulatum, 355
habit, 345–348
poisoning by, 343
treatment of, 343–344
pulvuratum, 355
tolerance to, 344–345
use of, in cantharidin poisoning, 204
in lead colic, 130
Optic nerve, effect of quinine on, 701
Optical isomerism, 21
Optochin, 704
Orange, bitter, peel, 216
vitamin C content of, 603
Ordeal bean, 451
"Organic" iron, 107
Organotropism, 772
Oridine, 76
Oriental sore, 162
Orizaba jalap root, 246
Ornithin, 697
Ornithosis, 746
Ornithuric acid, 696
Orpiment, 165
Ortal, 319
Orthocaine, 422
Orthocresol, 783
Orthoform, 422
Ortho-iodobenzoic acid, 697
Oscine, 464
Osmic acid, 151
Osmotic pressure, 44
Osteitis fibrosa, 551
Osteoblasts, 551
Osteoclasts, 551
Osteomalacia, 60, 61, 605, 608
Ouabagenin, 616
Ouabain, 616, 640
Ouabainum, 640
Ouabaio, 612, 616
tree, 612

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Ovale malaria, 704
Ovoflavin, 594
Ovum, effect of quinine on, 699
Ox gall, 224
Oxalates, 67
  poisoning by, 62
Oxalic acid, 91
Oxford unit, of penicillin, 745
Oxide, of magnesium, 243, 246
Oxidum nitrosum, 300
Oxophenarsine, 183-184
Oxybenzoic acid, 693
Oxycarbanil, 683
Oxygen, 92-95
  blood content, 93
  preparations of, 96
  therapeutic use of, 94–95
  toxicity of, 95
Oxygen consumption, effect of ingestion of water on, 46
Oxygenium, 96
Oxymel scillæ, 641
Oxynarcotine, 329
Oxysantonins, 763
Oxytocin, 531
Oxyuriasis, 757
Ozone, 95–96

P

Pain, referred, 199–200
Painters' colic, 126
Palsy, lead, 126–127
Paludrine, 717
Pamaquinæ naphthoas, 716
Pamaquine, 714–716
  chemistry of, 714
  naphthoate, 716
  preparations of, 716
  therapeutic uses of, 715
  toxicity of, 715
Pamaquinum, 716
Pancreas, function of, 558
Pancreatic ferments, 221
Pancreatin, 221
Pancreatrophic hormone, of pituitary, 530
Pannic acid, 758
Pansy, oil of, 209
Pantopon, 351
Pantothenic acid, 598–599
Papain, 222
Papaver somniferum, 329
Papaveramine, 329
Papavarine, 329, 330, 332, 349–350
  therapeutic use of, 354
Papaya, 222
Paprika, as source of vitamin C, 603
Para-aminobenzene sulfonamide, 726, 742
Para-aminobenzoic acid, 600, 733
Para-aminophenol, 674
Parachlorometacresol, 784
Paracodin, 350
Paradihydroxystilbene, 566
Paraffin, 195
  liquid, 232
Paraffinum, 195
  durum, 195
Paraform, 810
Paraguay tea, 394
Paraldehyde, 313
  dose of, 325
  use of, in alcoholism, 265
    in delirium tremens, 264
    in obstetrics, 326
Paraldehydum, 315
Paralysis, from lead, 126
Para-oxybenzoic acid, 693
Pararosaniline, 802
Parasiticides, copper as, 117
Parasitotropism, 772
Parasympathetic system, depressants of, 463–485
  stimulants of, 440–462
Parathyroid gland, 549–552
  extracts of, 550–552
  hormone of, 549–552
    preparations of, 552
    therapeutic use of, 551–552
  relation of, to calcium metabolism, 550
Para-toluene sulphonchloramide, 800
Paredrine, 505
Paredrinol, 505–506
Paregoric, 213, 352, 355, 356, 697
Paresis, 185
Paris green, 166
Parkinsonism, use of amphetamine in, 501
  use of hyoscine in, 481
Paroxysmal auricular fibrillation, use of quinidine in, 709
Parrish's food, 115
Pathological conditions, effects of on drug action, 28
Pathology, relation of, to pharmacology, 14
Patulin, 754
Paullinia sorbilis, 394
Pawpaw, 222
Payta, 659
Paytanine, 659
Paytine, 659
Pectin, 820
Pellagra, 595–596
  treatment of, 597
    use of pyridoxine, in, 598
Pelletierinæ tannas, 768
Pelletierine, 759
  tannate, 759
Pellets, 32, 38
  of hormones, 527
  of testosterone, 572
Pellitory, 220
Pemphigus, 557
Penatin, 754
Penicillin, 743–751
  absorption of, 746
  action of, 745
  B, 754
  chemistry of, 744
  excretion of, 746
  F, 744
  G, 744
  history of, 743
  K, 744
  oral, 751

Bharatiya Vidya Bhavan, New Delhi Collection

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Penicillin, therapeutic use of, 747
toxicity of, 747
X, 744
Penicillinase, 746
Penicillium notatum, 743
patulum, 754
Penillic acid, 744
Pennyroyal, 209
Pental, 293
Pentamethylentetrazol, 392
Pentaquine. *See* SN 13, 276.
Pentnucleotide, 579–580
use of, in agranulocytosis, 677
Pentobarbital, 319, 327
sodium, 319, 327
soluble, 327
Pentothal, 319
use of as anesthetic, 326–327
Peperidinomethyl benzodioxan, 515
Pepper, black, 220
cayenne, 220
group, 220
Peppermint, 216
Pepsin, 220
assay of, 40
Percaine, 414
Perchlorates, as oxidizing disinfectants, 795
Perfringens antitoxin, 41
Perfume, volatile oils as, 207
Pericarditis, constrictive, use of digitalis in, 637
Periostitis, in mercury poisoning, 139
in phosphorus poisoning, 188
Periploca graeca, 612, 616
Periplogenin, 616
Periston, 51, 820
Peritonitis, use of penicillin in, 748
Permanganate, of potassium 791–792
Pernoston, 319
Perosis, on chicks, 601
from manganese deficiency, 148
Peroxidase, inhibition of, by peroxidase, 665
Peroxide, of hydrogen, 790–791
Perpolitiones oryzæ, 591
Pethidine, 358–361
Petrolates, 195
Petrolatum, album, 195
liquidum, 245
leve, 245
Peyote, 362
Pfeiffer bacillus, 744
Phanodorn, 319, 328
Pharmacognosy, 15
Pharmacological action, 20
general theories of, 19
Pharmacological syndromes, 21
Pharmacology, definition of, 13
relation of, to other medical sciences, 13–15
Pharmacopoeia, 35
biological assay in, 39
preparations of, 35
Pharmacy, 15
Pheasant's eye, 612
Phemerol, 778
Phemitone, 327
Phemitonum, 327
Phenacaine, 413–414
Phenacetine, 674, 686, 687
toxicity of, 676
Phenacetinum, 687
Phenanthrene, derivatives of, veratrine-action of, 655
Phenarsone sulfoxylate, 184
Phenazone, 673, 686, 687
Phenazonum, 687
Phenetidines, 674
Phenobarbital, 317, 320–327
soluble, 320, 327
Phenobarbitalum, 327
Phenocoll, 674
Phenol liquefactum, 782
substituted, 783–784
toxicity of, 778–779
use of, as disinfectant, 778–782
Phenolphthalein, 235
preparations of, 245–246
Phenolsulfonphthalein, 235
for renal function test, 822
Phenolsulfonphthaleinum, 822
Phenoltetrachlorophthalein, 235
Phenothiazine, 757, 767
Phentetiothalein, 235
Phenylacrylic acid, 464
Phenylcarbylamine, 206
Phenyldimethylpyrazolon, 673
Phenylethylhydantoin, 374
Phenylhydrargyri nitras, 787
Phenylhydrazine, 673
Phenylisopropylamine, 500
Phenylis salicylas, 695
Phenylmercuric borate, 787
chloride, 787
nitrate, 787
picrate, 787
Phenylquinoline carboxylic acid, 669
Phenylsalicylate, 687–688
Phenytoin sodium, 373–377
Phlorhizin, 659
Phloridzin, 659
Phloroglucin, 758
Phloroglucinbutyric acid, 758
Phorphas, sodii, effervescens, 246
Phosgene, 206
Phosphatase, blood, in rickets, 605
Phosphates, 66–67
action of, in body, 242
blood, effect of parathyroid extract on, 550
of sodium, 243, 246
Phosphine, 189
Phosphoric acid, 67, 87, 91
Phosphorus, 187–190
blood, in rickets, 605
poisoning by, copper as antidote in, 117
symptoms of, 188
treatment of, 189–190
radioactive, 152, 190
use of therapeutically, 663
relation of, to calcium, 60
therapeutic use of, 190
toxicology of, 188–189

Bharatiya Vidya Bhavan, New Delhi Collection

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Phosphorus, sequisulfide, 188
Phosphuretted hydrogen, 189
Phthalylsulfathiazole, 730
Physiological salt solution, 51
Physiology, relation of, to pharmacology, 13
Physostigma venenosum, 451
Physostigmine, 451–456
  antagonism of magnesium to, 65
  therapeutic uses of, 455
Phytin, 600
Phytosterol, 606
Picramic acid, 785
Picric acid, 785
Picropodophyllin, 236
Picrotin, 389
Picrotoxin, 389–391
  use of, in barbiturate poisoning, 324, 391
Picrotoxinin, 389
Pigmentation, in arsenic poisoning, 168
Pills, 37
Pilocarpine, 459–462
  therapeutic uses of, 461
Pilocarpus, 459
Pilulæ, 37
Pimpernel, 221
Pimpinella anisum, 216
Pine tar, 806
Pineapple, 221
Pink root, 764
Pinus palustris, 805
Pinworm, 757
Piper methisticum, 220
Piperidine, 220, 428
Piperine, 220
Piperinic acid, 220
Pitocin, 531, 535
Pitressin, 531, 533
Pituitarium posterium, 540
Pituitary, action of, in female reproduction, 567
  anterior lobe of, 527–531
    extracts of, 527–531
  posterior lobe of, 531–540
    assay of, 39
Pituitrin, 531–540
Pituri plant, 429
Pityriasis steatoides, 805
Pix liquida, 806
Pix pini, 806
Placenta, function of, 568
  as source of antibodies, 819
Plantago seed, 244
Plantain, 244
Plasma, human blood, 820
Plasmochin. *See* Pamaquine.
Plasmodium falciparum, 704
  malariæ, 704
  ovale, 704
  vivax, 704
Plasmoquine. *See* Pamaquine.
Plaster, adhesive, 196
  court, 196
  isinglass, 196
  lead, 196
Plasters, 29, 38, 196
Plasters, cantharidin, 204
  mustard, 203
Platinum, 147
Plumbi acetas, 131
Plumbism, 124–129
Pneumoencephalography, 94
Pneumonia, use of digitalis in, 635
    of oxygen in, 94
    of penicillin in, 748
    of sulfonamides in, 727, 737, 739
Podophyllotoxin, 236
Podophyllum, 236
Poison ivy, 205
  use of permanganate in, 792
Poison oak, 205
poisoning, with caustic alkalies, 82
  by phenol, 782
  use of demulcents in, 192
  See also under specific drugs.
Poisons, definition of, 13
  protoplasmic, 18
  See also specific drugs.
Polycythemia, induced by cobalt, 149
  treatment of, 663
Polygala senega, 656
Polyneuritis, 591–592
Polyploidy, induction of, by colchicine, 669
Polyuria, following use of salicylates, 691
Pomegranate, 759
  preparations of, 768
Pontocaine, 414
Poppy-seed oil, iodized, 78
Porter, 268
Posterior lobe, of pituitary, 531–540
Posterior pituitary hormone, 531-540
  action of, 532–540
  chemistry of, 531–532
  preparations of, 540
  therapeutic use of, 539
Posterior pituitary liquid, 531–540
Pot curare, 423
Potash, as styptic, 80
Potassii acetas, 84
  bicarbonas, 83
  bitartras, 282
  bromidum, 373
  carbonas, 83
  chloras, 796
  citras, 84
    effervescens, 84
  iodidum, 77
  nitras, 53
  permanganas, 792
  et sodii tartras, 246
Potassium, action of, on heart, 54
  anti-curare action of, 426
  arsenite, 175
  bicarbonate, as antacid, 81
  bichromate, 148
  bismus tartrate, 158
  blood content of, 53
  chlorate, 794–796
  chloride, as diuretic, 52
  citrate, 84
  ferrocyanide, 101
  hexatantalate, 165

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Potassium, hydrate, 83
iodide, as diuretic, 52
mercuric iodide, 786
myronate, 203
permanganate, 791–792
use of, in poison ivy dermatitis, 205
rôle of, in nerve conduction, 54
salts of, 53
therapeutic use of, 55
toxicity of, 54
Potato, 657
Poultices, 202
mustard, 203
See also Cataplasma.
Powders, 38
dusting, 194
P-P factor, 595–597
Praseodymium, 152
Pregnancy, effect of, on use of drugs, 25
use of calcium in, 61
of iodides in, 74
of vitamin D in, 608
Pregnandiol, 568
Primula obconica, 205
Privine, 507
Proactinomyces gardneri, 753
Proactinomycin, 753
Procaine, 412
use of, intravenously, 416
Proflavinæ sulphas, 802
Proflavine, 801
sulfate, 801
Progesterone, 570–571
physiology of, 568
preparations of, 571
therapeutic use of, 570
Progestin, 570
Prolactin, 529
Promin, 731
Prominal, 327
Promizole, 731
Prontosil, 726
Propadrine, 504
Propionyl choline, 447
phenetidine, 674
Propyl alcohol, 268
use of, as disinfectant, 778
Propyl piperidine, 428
Propylene, 304
Propylthiouracil, 548–549
Prostigmin, 456
Protamine, zinc insulin, 561
Protargol, 789
Protectives, 193–197
Protein, hydrolysates of, 821
metabolism of, in anesthesia, 283
Protein silver, 789
Prothrombin, 581, 582
relation of to vitamin K, 610
Protocurarine, 423
Protocuridine, 423
Protocurine, 423
Protopine, 329
Protoplasm poisons, 18
Protoveratridine, 654
Protoveratrine, 654, 656
Provitamin A, 585–586
Provitamin, D, 607
Prunus laurocerasus, 663
serotina, 216
virginiana, 216
Prussic acid, 663
Pseudaconitine, 652
Pseudoergotinine, 509
Pseudohyoscyamine, 464
Pseudojervine, 654
Pseudomonas aeruginosa, 753
Pseudomorphine, 329
Psoriasis, 548
use of chrysarobin in, 803
use of vitamin D in, 608
Psychosis, following use, of bromides, 369
of iodoform, 797
of quinacrine, 712
Psychotria ipecacuanha, 717
Psychotrine, 717
Psyllium, as laxative, 244
Pulse rate, effect of alcohol on, 257
of anesthetics on, 275
of chloroform on, 275
of epinephrine on, 488
of ether on, 275
of nitrites on, 643–644
Pulveres, 38
Pulvis chiniofoni, 725
cretæ aromaticus cum opio, 64
compositus, 63
effervescens compositus, 246
ipecacuanhæ et opii, 721
Punica granatum, 759
Punicine, 759
Pupil, action of atropine on, 469
in anesthesia, 280
effect of ergot on, 513
regulation of, 435
Purgatives, 228–247
action of, 229
anthracene, 233–235
classification of, 228
contraindications to use of, 238
drastic, 236
mercury as, 139–140, 142
revulsive action of, 231
symptoms of, 228
therapeutic use of, 237–238
See also under specific items.
Purines, 394
Purple foxglove, 612
Purpura, 62
Purpurea glucoside A, 615
B, 615
Purpurea glycosides, 615
Pustulants, 197
Putrescin, 507
Pyelitis, 82
use of silver salts in, 134
Pyelography, 77
Pyocyanase, 753
Pyocyanin, 753
Pyramidon, 673
Pyrethrum, 220, 814
Pyribenzamine, 521
Pyridine, 428
Pyridoxine, 597–598

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Pyrocatechin, 781, 805
Pyrogallol, 802
Pyroxylin, 197
Pyroxylinum, 197

Q

QUARTAN malaria, 704
Quassia, 219
amara, 219
Quassiins, 218
Quebrachamine, 659
Quebrachine, 659
Quebracho, 659
blanco, 659
Quillaja saponaria, 656
Quinacrinæ hydrochloridum, 714
Quinacrine, 711–714
absorption of, 712
excretion of, 712
hydrochloride, 711–714
methyl sulfonate, 713, 714
preparations of, 714
soluble, 714
therapeutic use of, 714
toxicity of, 712
Quince, seeds of, 193
Quinetum, 716
Quinidinæ sulfas, 711
Quinidine, 703, 708–711
action of, 709
dosage of, 710
preparations of, 711
sulfate, 708–711
therapeutic use of, 709
Quininæ æthylcarbonas, 707
et æthylic carbonas, 708
bisulfas, 707, 708
hydrochloridum, 707
sulfas, 707, 708
tannas, 708
et ureæ hydrochloridum, 707
Quinine, 697–708
action of, 698–701
administration of, 706
as antipyretic, 673
as bitter, 707
didhydrochloride, 706, 707
dosage of, 706
as ecbolic, 707
ethylcarbonate, 706, 707
excretion of, 703
idiosyncrasy to, 702
as local anesthetic, 412, 707
preparations of, 705
as sclerosing agent, 707
sulfate, 706, 707–708
tannate, 706
therapeutic use of, 704
and urea hydrochloride, 707
as local anesthetic, 415, 418
Quinoline, 698
Quinoline, as antipyretic, 673
Quinoxyl, 723
Quinuclidine ring, 698

R

RABIES, use of vaccine in, 816
Racéphedrine, 499
Radium, 152
Ranunculaceæ, 205
Ratsbane, 176
Realgar, 165
von Recklinghausen's disease, of bone, 551
Rectum, drugs and, 31
Recurrent fever, 182
Reduced iron, 114
Reflexes, effect of alcohol on, 255
of anesthetics on, 273
of barbiturates on, 317
of bromides on, 367
Refrigeration, as method of anesthesia, 421
Remijia bark, 697
Remote effects, of drugs, 18
Renal insufficiency, and calcium abosrption, 60
Renal lithiasis, use of aluminum salts in, 122
Renoflavin, 594
Reproductive system, relation of pituitary to, 528
Resina podophylli, 246
Resins, 34
Resistance, development of, by trypanosomes, 186
Resorcin, 805
Resorcinol, 805
monacetate, 805
Respiration, effect of alcohol on, 256
of amyl nitrite on, 645
of anesthetics on, 273
of arsenic on, 170
of barbiturates on, 317
of bromides on, 367
of caffeine on, 396, 398
of carbon dioxide on, 98
of iodides on, 70
of morphine on, 334
of salicylates on, 690
of strychnine on, 385
Reticulocytes, effect of liver on, 574
Retina, effect of naphthol on, 804
effect of quinine on, 701
Reversal, of epinephrine action, by ergotoxine, 487
Reversible action, of drugs, 17
Rhamnose, 614
Rhamnus purshiana, 245
Rheum, 245
Rheumatic fever, use of salicylates in, 693–694
use of sulfonamides in, 740
Rheumatic heart disease, use of digitalis in, 632
Rheumatism, use of neocinchophen in, 672
Rhodanase, 666
Rhoeadine, 329
Rhubarb, 234
Rhus toxicodendron, 205

Bharatiya Vidya Bhavan, New Delhi Collection

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Rhus venenata, 205
vernicifera, 205
Riboflavin, 593–595
chemistry of, 594
effects of deficiency of, 594
preparations of, 595
therapeutic use of, 595
Riboflavina, 595
Riboflavinum, 595
Ribose, 594
Rice polishings, 591
Ricin, 822
Ricinoleic acid, 231
Ricinus communis, 822
Rickets, 605, 608
Rickettsial diseases, use of aminobenzoic acid in, 600
Ringer's solution, 51
Ringworm, use of chrysarobin in, 803
Riodine, 76
Risus sardonicus, 380
Rochelle salt, 239, 246
Rocky-Mountain spotted fever, 600
Roentgenography, drugs used in, 76–77
Rooms, disinfection of, 777, 810
Rosacea, use of resorcin in, 805
Rosæ, 216
Rosaniline, 802
Rosmarini, 216
Rosemary, 216
Rottlerin, 758
Roundworm, 757, 763
Roxenol, 784
Royal jelly, 599
Rubefacients, 197
alcohol as, 265
ammonia as, 85
chloroform as, 291
mustard as, 203
turpentine oil as, 202
Rubidium, salts of, 55
Rubijervine, 654
Rutin, 604

S

SABADILLA, 654
Sabadine, 654
Sabadinine, 654, 656
Sabatrine, 654
Sabinol, 207
Saccharin, 215
Saccharinum solubile, 215
Sacharomyces sicci, 591
Safrol, 207
Sage, oil of, 209
Sajodin, 76
Salanaceæ, 263
Salep, 193
Salicin, 687, 692
Salicinum, 696
Salicyl alcohol, 692
phenetidine, 674
Salicylates, 687–696
dose of, 694–695
fatalities from, 689
keratolytic action of, 695
local action of, 687–688
Salicylates, nephrotoxic action of, 691
preparations of, 695–696
symptoms from use of, 688
therapeutic use of, 693
use of, as preservative, 695
Salicylic acid, 687–695
use of, as antiseptic, 687–688, 785
Salicyluric acid, 692
Saligenin, 692
Saline cathartics, preparations of, 246
therapeutic use of, 242–244
Saline diuretics, therapeutic use of, 52
Salipyrine, 673
Saliva, secretion of, 467
Salivation, in mercury poisoning, 139
Salmonella, 746, 753
Salol, 687, 688
Salt solutions, balanced, 60
Saltpeter, 53
Salts, as diuretics, 52
effect of hypertonic, 49
effervescent preparations of, 246
iodized, 74
physiology of, 43–46
therapeutic use of, 45, 50
Salumin, 122
Salvarsan, 180–182
Salves, 29
phenolated, 782
Salyrgan, 143
Salysal, 693
Samandaridine, 389
Sandoptal, 320, 328
Sanocrysin, 147
Santonin, 757, 761–763
preparations of, 768
Santoninum, 768
Sapo animalis, 196
durus, 196
mollis, 196
viridis, 196
Sapogenins, 657
Saponaria officinalis, 656
Saponin, 656–657
Sapotoxin, 656–657
Sarmentose, 614
Sarsaparilla, 656
Sassafras, 193
medulla, 193
pith, 193
Sassy bark, 612
Satinwood, 205
Savine, oil of, 207, 209
Scabies, use of balsam of Peru in, 807
use of pyrethrum in, 814
use of sulfur in, 232, 806
Scammoniæ resina, 246
Scammony, 236
mexican, 246
Scarlet fever, 740
antitoxin, 819
streptococcus toxin, 816
Scarlet R, 800
red, 800
sulfonate, 800
Scheele's green, 166
Schick test, 821

Bharatiya Vidya Bhavan, New Delhi Collection

In Public Domain. Digitization by eGangotri and Sarayu Trust

Schistosomiasis, 163, 758
Schizogony, 704
Schleich's solution, 419
Schœnocaulon officinale, 654
Schultz-Charlton test, 821
Schweinfurt's green, 166
Scilla, 640
  maritima, 612, 616
Scillaren, 616
  effect of, on kidney, 625
Scillaridine, 616
Sclerosing agent, 651
  quinine-urea as, 707
Scoparius, 403
Scopine, 463
Scopola, 657
Scopolamine, 463–464, 476–477, 484
  use of, in anesthesia, 309
Scopolia, 464
Scopoline, 464
Scrub typhus, 600
Scurvy, 602, 604–605
Seatworm, 757
Seborrhea, use of resorcin in, 805
Secale cereale, 507
Seconal, 320
Sedatives, 310–327
  preparationsıf, 327–328
  references to, 328
  tolerance to, 314
  use of apomorphine as, 364
Seidlitz powder, 243, 246
Selenium, 150
  oxychloride, 151
Semecarpus anacardium, 206
Sempervirine, 428
Senna, 234
  preparations of, 245
Sennae fructus, 245
Sensibamine, 509
Septentrionaline, 653
Sera, 815–820
  antitoxic, 818
  blood, 820
  immune, 818
  standardization of, 41
Serum antidysentericum (shiga), 820
  antimeningococcicum, 820
  antipneumococcicum, 819, 820
  humanum normale, 820
  immune morbillosi humanum, 819
    scarlatinæ humanum, 819
Sesame oil, 195
Sesquiterpenes, 207
Setons, 197
17-hydroxycorticosterone, 553
Sevum, 195
Sex, effect of, on drug action, 25
  hormones, 563–564
    female, 564–571
    male, 571–573
Shale, bituminous, 806
Sharkskin, 594
Sherry, 268
Shigella paradysentery, 739
  use of sulfonamides in, 729
Shock, surgical, 557
Shock, use of blood plasma in, 820
Silver, 131–135
  arsphenamine, 183
  colloidal preparations of, 789–790
  lactate, 789
  nitrate, use of, as antiseptic, 788–789
  picrate, 789
  salts of, 131–135
    poisoning by, 132
  use of, as antiseptic, 788
Silvol, 789
Simmonds' disease, 529
Sinapis nigra, 203
Sinigrin, 203
Sippy treatment, 81
Size, effect of, on dose, 24
Skin, antiseptics for use on, 802–807
  cancer of, from arsenic, 169
  disinfectants of, 774
  disorders of, ointments used in, 144
    use of arsenic in, 175
    use of disinfectants in, 775
    from zinc, 120
  effect of alcohol on, 257
    of alkalies on, 79
    of ammonia on, 85
    of arsenic on, 170–171
    of camphor, on 210
    of iodine on, 73
    of mercury on, 139
    of resinous purges on, 237
    of sulfur on, 232
    of tartar emetic on, 161
    of vitamin A deficiency on, 587
  eruptions of, from hypnotics, 314
    from iodides, 71
    from phenolphthalein, 235, 236
    from salicylates, 689
    from sedatives, 314
  irritants, 197–198
Skiodan, 77
Smallpox, immunity to, 815
Smelling salts, 85
Smilax, 656
Smoking, effect of, 438–440
"SN 7,618," 716
"SN 13,276," 717
Snake-bite, use of permanganate in, 792
Soap, castile, 196
  curd, 196
  liniment, 196
  soft, 196
  use of, as disinfectant, 777
    as suppository, 233
Soap-bark, 656
Soap-root, 656
Soap-wort, 656
Sobisminol, 158
Soda. *See* Sodium bicarbonate.
Sodii benzoas, 697
  bicarbonas, 83
  boras, 794
  biphosphas, 91
  bromidum, 373
  carbonas, 83
  citras, 84
  morrhuas, 652

Bharatiya Vidya Bhavan, New Delhi Collection

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Sodii nitris, 650
phosphas, 246
acidus, 91
salicylatis, 695
sulfas, 246
Sodium acid phosphate, 67, 91
antagonism of, to calcium, 61
arsanilate, 178
aurothiosulfate, 147
barbitone, 327
benzoate, 696–697
bicarbonate, 80
as antacid, 81
use with antipyretics, 676
use with salicylates, 694
biphosphate, 91
bismuthate, 158
borate, 792
cacodylate, 178
chloride, as diuretic, 52
metabolism of, 48
preparations of, 51
rôle in adrenal activity, 555
use in Addison's disease, 556
use in adrenal insufficiency, 553, 556
citrate, 84
cyanide, 665
dehydrocholate, 223
fluorosilicate, 68
formaldehyde sulfoxalate, 144
gynocardate, 651
hypochlorite, 799–800
hyposulfite, 811
iodophippurate, 77
iodopyridon acetate, 77
lactate, 84
mandelate, 809
morrhuate, 651
nitrite, 647
use in cyanide poisoning, 665
perchlorate, 795
peroxide, 791
phosphate, use as cathartic, 239, 243
potassium tartrate, 239
salicylate, use as antiseptic, 785
succinate, use in barbiturate poisoning, 324
sulfate, 239
sulfite, 811
sulfo-oleate, 806
thiosulfate, 811
use in cyanide poisoning, 665
toxicity of, 61
Soft petrolate, 195
soap, 196
Solanidine, 657
Solanine, 656–657
Solanum, 657
Solargentum, 789
Solutol, 783
Solveol, 783
Soporifics, 310–327
Sowbread, 656
Spanish fly, 204
Sparteine, 428
Spartium scoparius, 428
Spas, therapeutic value of, 46, 49, 50
Spearmint, 216
Spectacled eye, 600
Spermaceti, 195
Spermatogenesis, effect of lead on, 126
Spermatozoa, effect of quinine on, 699
Spider-bite, 62
Spigelia, 764
maritima, 764
Spinal anesthesia, 419
Spirillosis, use of arsphenamin in, 182
use of bismuth salts in, 157
Spirits, 37
of ammonia, 85, 86
of camphor, 212
of juniper, 217
of nitroglycerin, 647
of volatile oils, 216–217
Spiritus, 37, 216
ætheris nitrosi, 650
æthylis nitritis, 650
ammoniæ aromaticus, 86
chloroformi, 294
frumenti, 268
glycerylis trinitratis, 649
vini vitis, 268
Spleen, effect of quinine on, 700, 703
Sporogony, 704
Sporotrichosis, 74
Sprue, treatment of anemia of, 602
Squills, 612, 616
compound syrup of, 162
expectorant action of, 636–637
Standard preparations, 39
See also under specific drugs.
Straphylococcic infections, use of penicillin in, 747
Staphylococcus antitoxin, 819
aureus, 745
infections by, use of sulfathiazole in, 728, 737
toxoid, 817
Starch, use of, as demulcent, 192, 193
as dusting powder, 194
Stavesacre, 652
Stearoptenes, 207, 209
Sterculia acuminata, 394
Sterility, 548
use of vitamin E in, 610
Sternutatories, 29
Sternutators, 206
Stibamine, 164
urea, 164
Stibanilic acid, 164
Stibophen, 163, 165
Stibosan, 164
Stigmasterol, 554
Stilbamidine, 186
Stilbestrol, 566
Stilbœstrol, 570
Stimulants, of central nervous system, 379–404
of parasympathetic activity, 440–462
Stimulation, by drugs, 15
Stomach, acid of, 89
action of acids on, 87
action of alkalies on, 79
action of demulcents on, 192

Bharatiya Vidya Bhavan, New Delhi Collection

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Stomach, disorders of, use of bismuth salts in, 156–157
effect of anesthetics on, 281
of bismuth salts on, 155
of heavy metals on, 105
of mercury on, 139
of volatile oils on, 208
in phosphorus poisoning, 189
preparations of, 578–579
assay of, 40
Stomachic, use of quinine as, 707
Stomachus pulveratus, 579
Stomatitis, mercurial, 136, 139
Storax, 807
Stovaine, 422
Stovarsol, 185, 722
Stramonium datura, 463
preparations of, 483
use of, in parkinsonism, 482
Straub test, 338
Streptamine, 751
Streptidine, 751
Streptobiosamine, 752
Streptococcus, anerobic, 708
enterococcic, 738
fecalis, 602, 739
infection by, use of penicillin in, 747
use of sulfanilamide in, 726, 737
viridans, 746
Streptomycin, 751–753
Streptothricin, 753
Strongyloides stercoralis, 757
Strongyloidiasis, 757
use of gentian violet in, 767
Strongyloidosis, 757
Strontium, 64
Strophanthidin, 615, 616
Strophanthin, assay of, 39, 40
therapeutic use of, 640
Strophanthinum, 640
G, 640
Strophanthus, 640
assay of, 40
gratus, 616
hispidus, 612, 615
kombé, 612, 640
Strychninæ sulfas, 388
Strychnine, 379–389
action of, 381–387
poisoning by, 388
preparations of, 388–389
as stomachic bitter, 386
synergism of, with physostigmine, 455
therapeutic uses of, 387–388
use of, in alcoholic intoxication, 265
Strychnos toxifera, 423
Stupe, turpentine, 202
Styptic, aluminum as, 122
iron as, 113
Styrax, 807
benzoin, 807
Suberic acid, 616
Submaxillary gland, innervation of, 433
Substituted ammonias, 58
Subtertian malaria, 704
Subtilin, 753
Succinate, 68
Succinchlorimide, 813
Succinic acid, 68
Succinylsulfathiazole, 730, 742
Succinylsulfathiazolum, 742
Sucrose. 214
Sudorific, pilocarpine as, 461
Suet, 195
Sugar, 214
of milk, 214
Sulamyd, 730
Sulfa drugs, 725–742
Sulfabenzamine, 731
Sulfacetimide, 730
Sulfadiazine, 728, 742
Sulfadiazinum, 742
sodicum, 742
sterile, 742
Sulfaguanidine, 729, 742
Sulfaguanidinum, 742
Sulfamerazine, 728–729, 742
Sulfamidochrysoidin, 726
Sulfamylon, 731
Sulfanilamide, 725, 727, 742
derivatives of, 725–742
Sulfanilamidum, 742
Sulfanilyl guanidine, 729, 742
sulfanilamide, 731
Sulfapyrazine, 729
Sulfapyridine, 727, 742
Sulfapyridinum, 742
sodicum sterile, 742
Sulfarsphenamine, 183
Sulfasuxidine, 730, 742
Sulfathiazolum, 742
sodicum, 742
sterile, 742
Sulfate, action of, in body, 242
of magnesium, 239, 246
of sodium, 239, 246
Sulfathiazole, 727–728, 742
Sulfhemoglobin, 69
Sulfides, 68
Sulfobromophthalein, for hepatic function test, 822
Sulfobromophthaleinum sodicum, 822
Sulfoichthyolate, preparations of, 806
Sulfoichthyolic acid, 806
Sulfonal, 313
Sulfonamide derivatives, 725–742
acetylation of, 732
action of, 732
preparations of, 742
therapeutic use of, 737
toxicity of, 734
use of, locally, 740
prophylactically, 740
Sulfonethylmethane, 313
Sulfonmethane, 313
Sulfur, compounds of, as antiseptics, 806
dioxide, as disinfectant, 811
præcipitatum, 245
precipitated, 806
sublimatum, 245
use of, as laxative, 232
Sulfuretted hydrogen, 69
Sulfuric acid, 87, 90
Sulfurous acid, anhydride of, 811

Bharatiya Vidya Bhavan, New Delhi Collection

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Sulphacetamidum, 742
solubile, 742
Sulphadiazina, 742
solubilis, 742
Sulphaguanidina, 742
Sulphanilamidum, 742
Sulphapyridina, 742
solubilis, 742
Sulpharsphenamina, 187
Sulpharsphenamine, 183
assay of, 40
Sulphas, sodii, 246
effervescens, 246
Sulphates, use of, as purgatives, 242
Sulphathiazolum, 742
solubile, 742
Sulphides, 68
Sulphur, flowers of, 245
præcipitatum, 245
sublimed, 245
use of, as laxative, 232
Sulphurated potassium, 70
Sulphuretted hydrogen, 69
Sulphuric acid, 87, 90
Sundew, 221
Sunlight, antirachitic action of, 607
Suppositoria, 37
glycerini, 245
Suppositories, 30, 37
glycerin, 233
Suppositorium iodoformi, 798
phenolis, 782
plumbi compositum, 356
Suprarenine, 485
Suprifen, 507
Suramin, 186, 187
Surgery, antiseptics used in, 777–802
use of antiseptics in, 774
Surgical bismuth paste, 789
Sweat glands, action of epinephrine on, 492
Sweating, inhibition of, by atropine, 468
Sweet spirits, of niter, 648
Sympathetic system, stimilants of, 485–505
Sympathin, 494
Sympatol, 503
Syncope, in anesthesia, 278
Syndromes, heterogenous, 21
pharmacological, 21
Synephrin, 503
Synergism, 27
Synergists, 27
Synthalin, 457
Syntropan, 464, 482–483
Syphilis, arsenicals used in, 179–187
experimental, use of bismuth salts in, 157
use of bismuth salts in, 157–158
of iodides in, 74
of mercury in, 142
of penicillin in, 749
Syrup, 36, 214, 217
of citric acid, 92
Easton's, 115
of ferrous iodide, 78
of ipecac, 721
Syrup of ipecac, use in paroxysmal auricular tachycardia, 710
of Tolu, 807
of volatile oils, 217
Syrupi, 36
Syrupus, 214, 217
ferri phosphatis cum quinina et strychnina, 708
picis pini, 806
scillæ, 641
tolutanus, 807

T

Tabellæ diethylstilbestrolis, 569
stilbœstrolis, 570
Tablet triturates, 38
Tablets, 38
Tablettæ, 38
Tachycardia, auricular, use of digitalis in, 633
paroxysmal, use of quinidine in, 710
sinus, 710
ventricular, use of digitalis in, 637
use of quinidine in, 710
Tachyphylaxis, 498, 533
Tachysterol, 606
Tænia saginata, 757
solium, 757
Tæniasis saginata, 757
solium, 757
Taka-diastase, 222
Talc, 194, 197
Talcum purificatum, 197
Tamarinds, as aperient, 214
Tamarindus, 214
Tannal, 122
Tannate, of albumin, 226
Tannic acid, 224–226
preparations of, 227
Tannins, 224–226
Tapeworm, 757, 758, 759, 764
Tar, 771
as antiseptic, 805–806
Tarkaktogenos kurzii, 650
Tartar emetic, 160–162
Tartaric acid, 92
Tartrates, action of, in body, 242
of sodium and potassium, 239
Taste, drugs affecting, 214–220
Taurine, 222
Tea, 394, 402
Teeth, mottled, 68
Tellurium, 150
Temperature, body, in anesthesia, 282
effect of alcohol on, 262
of antipyretics on, 679
of mercury on, 141
of quinine on, 703
of saline cathartics on, 242
Temporary conditions, effect of, on drug action, 25
Teniacides, 757–769
Terpenes, 207
Terpin hydrate, elixir of, 352
Terpineol, 213
Terra silicea purificata, 197

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Tertian malaria, 704
Testicular hormone, 571
Testosterone, 572–573
Tetanus, 746
  antitoxin, 41, 819
  toxoid, 817
  use of avertin in, 306
Tetanus-gas gangrene antitoxin, 819
Tetany, parathyroid, 550
  treatment of, 62
  use of calcium salts in, 62
Tetracaine, 413–414
Tetrachlorethylene, 757, 766
  preparations of, 768
Tetrachlormethane, 768
Tetrachloroæ thylenum, 768
Tetrahydronaphthylamine, 661
Tetraiodophenolphthalein, 236
Tetraiodopyrrol, 798
Thalline, 673
Thallium, 150
  poisoning by, 150
Thebaine, 330, 349
Theelin, 565
Theelol, 565
Theobroma cacao, 196, 394
Theobromine, 394–402
Theocalcin, 400
Theocin, 394–404
Theon, 402
Theophylline, 394–402
Theories, of pharmacological action, 19
Therapeutics, definition of, 13
Thevetia neriifolia, 612, 616
Thevetin, 616
Thiaminæ hydrochloridi, 593
Thiamine, 591–593
  action of, 592
  effects of deficiency of, 591
  preparations of, 593
  rôle of, in etiology of cirrhosis, 261
  therapeutic use of, 593
Thigenol, 806
Thio-bismol, 158
Thiodiglycolchloride, 206
Thioglycollamide, 162-163
Thiopentone, 328
Thiouracil, 548–549
Thiourea, 549
Thorium, 152
  oxide, 152
Thorn apple, 463
Thorotrast, 152
Threadworm, 757
Thrombin, 582
Thrombocytopenia, following sulfonamide therapy, 735
Thromboplastin, 582
Thrush, 754
Thujon, 207, 210, 389
Thyme, oil of, 760
Thymol, 207
  iodide, 798
preparations of, 768
  use of, as anthelmintic, 760
    as antiseptic, 785
Thymolis iodidum, 798
Thyreoglobulin, 542
Thyroglobulin, 542
Thyroid gland, 540–548
  adenoma of, 73
  diseases of, 73
    use of iodine in, 73–74
  hormone, of, 540–548
Thyroideum, 548
Thyrotrophic hormone, of pituitary, 529
Thyroxin, 541, 542, 548
Thyroxinum, 548
Tigonin, 657
Time of administration, of drugs, 25
Tin, 149–150
Tinctura benzoini, 807
    composita, 807
  cinchonæ, 707
  colchici, 669
  digitalis, 640
  iodi, 78, 796
    mitis, 78, 796
  nucis vomicæ, 388
  opii camphorata, 355, 697
  tolutana, 807
Tincture, 37
  of iodine, 78
  of nux vomica, 387
  of volatile oils, 218
Toad, secretions of, 616
Tobacco, 438–440
  deleterious effects of, 439
  Indian, 429
Tocopherol, 609–610
Tolerance, 26
  acquired, 26
  to alcohol, 262
  to antipyretics, 675
  to arsenic, 173
  congenital, 26
  to drugs, 26
  to hypnotics, 314
  to quinine, 703
  to sedatives, 314
Tolu balsam, 697
Toluifera pereiræ, 807
Toluylendiamine, 662
Toot, 389
Totaquina, 707, 708
Totaquine, 705, 707
Toxalbumins, 822–823
Toxaxanthin, 585
Toxicodendrol, 205
Toxicology, 13
Toxins, use of, in immunization, 816
Toxinum diphthericum, 818
    califactum, 822
    detoxicatum, 818
    diagnosticum, 822
  scarlatinæ streptococcicum, 818, 822
  tetanicum, 818
    detoxicatum, 818
Toxisterol, 606
Toxitabellæ hydrargyri bichloridi, 786
Toxoids, 817
Trachoma, 737
Tragacanth, 192
Tragacantha, 193

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Trasentin, 464, 483
Trehalose, 507
Trematodes, 758
Treparsol, 722
Treponema pallidum, 746
Triasyn B, with liver, 590
preparations of, 590
Triazine arsonic acid, 186
Tribromœthanol, 305–306
Trichinella, 822
Trichloracetic acid, 91
Trichloroethylene, 293
Trichocephaliasis, 757
Trichomonas vaginitis, 184, 185
use of vioform in, 724
Trichophyton gypseum, 754
Trichuriasis, 757, 763
use of ficin in, 768
Trichuris trichiura, 757, 760
Tridione, 377–378
Trimethylamine oxide, 58
Trimethylethylene, 293
Trinitrophenol, 785
Trional, 313
Triorthocresyl phosphate, 784
Triphal, 147
Triphenine, 674
Triphenylmethane dyes, 802
Triphenyl phosphate, 784
Tritopine, 329
Triturationes, 38
Triturations, 38
Troches, 29, 38
Trochisci, 29, 38
Trochiscus morphinæ et ipecacuanhæ, 721
phenolis, 782
Tropacocaine, 405
Tropane, 463
Tropeines, 464
artificial, 477–479
Tropic acid, 463
Tropical diseases, use of antimony in, 162–164
Tropine, 463
Truxillyl-ecgonine, 405
Trypaflavine, 801
Trypanosomiasis, 163
drug therapy of, 185–186
use of bismuth salts in, 157
Tryparsamide, 184
Tryparsamidum, 187
Tsutsugamushi, disease, 600
Tuberculin, 821
potency of, 41
Tuberculinum pristinum, 822
Tuberculosis, as contraindication to use of iodine, 75
use of gold in, 147
use of sulfonamides in, 731
Tubocurare, 423
Tubocurarine, 423
Tularemia, 737, 738
Tungsten, 150
Turlington's balsam, 807
Turpentine, 202–203
Tutin, 389
Tutocaine, 415
Tutu, 389
T-wave, of electrocardiogram, effect of digitalis on, 626
Typhoid fever, 746, 752
use of antipyretics in, 684
Typhoid-paratyphoid vaccine, 817
Typhus, 600
use of DDT in prevention of, 814
vaccine for, 817
Tyramine, 506
Tyrocidine, 753
Tyrosine, 507
Tyrothricin, 753

U

Ulcers, corneal, 548
gangrenous, use of permanganate in, 792
gastric, from use of cinchophen, 672
peptic, 122
Uliron, 731
Ulmus, 193
Untraviolet light, as disinfectant, 813
irradiation with, 606
Umbelliferæ, 207
Uncinariasis, 757, 760
Undulant fever, use of sulfonamides in, 737
Unguenta, 29, 38
Unguentum, 195
acidi salicylici, 696
aquæ rosæ, 195
aquosum, 195
chrysarobini, 804
iodi, 78
paraffini, 195
phenolis, 782
picis pini, 805
simplex, 195
Unna's paste, 120
Upas tree, 612
Uracil, 507
Uradal, 373
Uranium, 150
Urari, 423
Urea, as diuretic, 53, 403
and quinine, as local anesthetic, 415, 418
stibamine, 164
Urethane, 314, 315
Urethanum, 315
Urethritis, use of acridine dyes in, 801
use of methenamine in, 808
Urginea, 641
scilla, 640
Uric acid, 58
excretion of, effect of conchophen derivatives on, 670
effect of salicylates on, 692
Urinary output, effect of water on, 47
Urine, alcohol content of, 256
alkalinization of, 81, 84
composition of, 49
effect of alcohol on, 262
of antipyretics on, 683
of cinchophen on, 671

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Urine, effect of digitalis on, 625
of iodides on, 71
of phenol on, 781
of salicylate on, 689
excretion of volatile oils in, 209
infections of, use of sulfonamides in, 739
lead content of, 126
in phosphorus poisoning, 189
volume of, effect of salicylates on, 691
Urography, 77
Urticaria, 62
Uterus, action of posterior-pituitary extract on, 535
effect of chloroform on, 282
effect of epinephrine on, 491
effect of ergot alkaloids on, 513
effect of ether on, 282
effect of hydrastinine on, 658
effect of morphine on, 341
effect of quinine on, 700, 702
Uva ursi, 403

V

Vaccination, 815
Vaccines, 815, 817
typhoid-paratyphoid, 817
Vaccinum rabies, 817
typho-paratyphosum, 817
typhosum, 817
vacinniæ, 818
variolæ, 818
Vaginitis, use of estrogens in, 569
Vagus, effect of quinine on, 700
Valerian, oil of, 213
Valeriana officinalis, 213
Vanadium, 150
Vanillin, 207, 218
Vanillinum, 218
Vasopressin, 531
Vegetable astrigents, 224
ferments, 221
Veratridine, 654
Veratrine, 654–656
Veratrum, 654
album, 654
sabadilla, 654
viride, 654
Verbascum 193
Veritol, 505
Vermicides, 757
Vermifuges, 757
Veronal, 316
Vesicants, 197
cantharidin as, 204
mustard as, 203
Vibrion septique, 746
Vinbarbital sodium, 328
Vincent's angina, 182
Vincent's infection, 747, 749
Vinegar, medicated, 37
of squill, 640
Vinethene, 292–293
Vinyl ether, 292
group, 698
Vioform, 724, 725, 798
Violet-green, 775
Viosterol, 606, 608
Vision, effect of quinine on, 701
effect of salicylates on, 690
Vitamin, antineuritic, 591
anti-ophthalmic, 584
anti-scorbutic, 602
Vitamin A, 584–590
assay of, 40, 588
chemistry of, 584
occurrence of, 586
preparations of, 589
unit of, 588
vitamers of, 586
Vitamin A_2, 586
Vitamin B complex, 590
Vitamin Bc, 602
Vitamin B_1, 591–593
assay of, 40
Vitamin B_2, 593–595
Vitamin B_6, 597–598
Vitamin B_{10}, 602
Vitamin B_{11}, 602
Vitamin C, 602–605
assay of, 40
Vitamin D, 62, 605–608
assay of, 41
and calcium metabolism, 60
chemistry of, 605–607
distribution of, 607
preparation of, 608
therapeutic use of, 608
toxicity of, 607
unit for, 608
Vitamin D_1, 607
Vitamin D_2, 606
Vitamin D_3, 606
Vitamin D_4, 607
Vitamin E, 609–610
Vitamin G, 593–595
Vitamin K, 610–611
antagonism of, to dicumarol, 581
use of, in dicumarol overdosage, 582
in salicylate poisoning, 689
vitamers of, 611
Vitamin, M,
Vitamin P, 604
Vitamini Bi, 593
Vitamini D concentratus, 608
Vitamins, 583–612
Vivax malaria, 704
Volatile oils, 35, 207
as flavoring agents, 215
poisoning by, 209
as urinary antiseptics, 808
Vomicine, 387
Vomiting, in anesthesia, 281
Vouacapoua aroroba, 803

W

Warts, 80
Washes, 37
Water, absorption of, 45
aromatic, 217–218
body content of, 43

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Water, disinfection of, 777
by chlorine, 813
by hydrogen peroxide, 791
as diuretic, 53, 403
effect of ingestion of, on cardiac putput, 47
on circulation, 47
on oxygen consumption, 46
excretion of, 45
extracellular, effect of alcohol on, 260
heavy, 46
metabolism of, 43–46
permeability of cells to, 45
preparations of, 47
therapeutic use of, 50
in fever, 46
Water dropwort, 389
hemlock, 389
Waterhouse-Friderichsen syndrome, 557
Wax, 195
Weight, effect of, on dose of drugs, 24
Whipworm, 757, 760, 763
Whiskey, 268
White hellebore, 654
White precipitate, 145
Wilkinson's salve, 806
Wines, 268
Wintergreen, 687
Witchhazel, 227
Wolfsbane, 652
Woorali, 423
Woorare, 423
Wormwood, oil of, 209
Wounds, healing of, and vitamin C, 604

X

Xanthine-oxidase, 594
Xanthines, 393–404
preparations of, 400, 403–404
Xanthopsia, following use of santonin, 762
Xeroform 789
Xerophthalmia, 587
Xerosis, 587
Xerostomia, 462
X-ray, use of iodine compounds as contrast media in, 76

Y

Yatren, 723, 724
Yaws, acetarsone in treatment of, 185
arsphenamine in treatment of, 182
Yeast, irradiated, 607
Yerba mate, 394
Yohimbehe tree, 659
Yohimbine, 659
Young's formula, 25
Youpon, 394
Yttrium, 152, 154

Z

Zeaxanthin, 585
Zephiran chloride, 778
Zinc, 118–121
in insulin, 558–559
peroxide, 791
salts of, 118
sulfate, 118
therapeutic use of, 119–120
Zinci peroxidum medicinale, 791
Zingiber, 216
Zirconium, 152
Zygadenus, 654

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